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CONTENTS

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Chromosome Size in Normal Rat Organs in Relation to B Vitamins, Ribonucleic Acid, and Nuclear Volume

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Rat chromosomes vary considerably in volume from one normal cell type to another. The relationship of their size to the concentration of the B vitamins and ribonucleic acid, and to nuclear volume, should aid in explaining the significance of the morphological differences between chromosomes of cancer cells and those of normal tissues (2, 6, 7) that are already evident by the third day of epidermal carcinogenesis in mice (5).

There is a direct relation between average chromosome volume and concentration of B vitamins in normal rat organs that promises to make more vivid our conception of the role played by the chromosomes as vital organelles in somatic cells. The study of cytoplasmic concentration of ribonucleic acid should allow us to determine whether excess amounts of nucleic acid in the cell and on the chromosomes could be responsible for the increased size noted in cancer chromosomes (2, 5, 6, 7). Since the greater size seems rather to be a reflection of a multiple structure, it is of interest to determine whether chromosomes of the same double nature as cancer chromosomes occur in normal organs. To this end a study of plasmosome numbers and nuclear volumes was made, although nuclear volume turned out to be not strictly proportional to the total volume of the mitotic chromosomes.

MATERIALS AND METHODS

The organs used in this study were taken from 4 rats,[1] of which Rat A was a 2 day old male of the Wistar strain, Rats B and C were adult Osborne-Mendel males bearing transplants of hepatoma 31, and Rat D was a Wistar male 84 days old.

In order to determine metaphasic chromosome volumes, nuclear volumes and plasmosome numbers of resting nuclei, acetocarmine preparations were made after fixation in Carnoy's fluid. The 25 best mitotic figures of metaphase or late prophase found in the preparations of each organ were drawn under oil immersion with a camera lucida at a drawing magnification of 3,000. An average chromosome volume was computed according to the method previously described (6, 7) for each of 350 approximately metaphasic figures. Depending on the variability of nuclear volume, 50 or 100 resting nuclei were measured with the aid of a camera lucida, millimeter ruler, and the fine adjustment of the microscope, and their volumes were calculated as the average of the volumes of a short cylinder and an ellipsoid of the dimensions found (7). When possible, the number of plasmosomes was counted in each resting nucleus measured. In so far as occasional fusion of plasmosomes was revealed by lobing of large plasmosomes, each lobe was counted as a single plasmosome. In addition, volumes were computed and plasmosomes were counted in 200 resting nuclei of regenerating liver and 400 nuclei of control adult livers that furnished the chromosomes of another study (3).

Ribonucleic acid was demonstrated in tissues by the histochemical method of Brachet (9). First, pieces of a number of organs of Rat D were preserved in Helly's fixative. Experimental slides of each organ were incubated in a solution of ribonuclease[2] of a concentration of 0.2 mgm. per cm.[3] in McIlvaine's

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[1] I am obligated for the animals as noted: Rat A, to Dr. Alfred Taylor, of the Biochemical Institute, The University of Texas, Austin; Rats B and C, to Drs. A. J. Dalton and J. W. Thompson, of the National Cancer Institute, Bethesda; and Rat D, to Dr. Edmond J. Farris, of the Wistar Institute of Anatomy and Biology, Philadelphia.

[2] For this ribonuclease, which was salt-free and 5 times recrystallized, I am greatly indebted to Dr. M. Kunitz, of the Rockefeller Institute for Medical Research, Princeton.

citric acid disodium phosphate buffer solution of pH 7.0, since Kunitz has found that the optimum pH range for ribonuclease is 7.0 to 8.3 (28). The incubation was allowed to proceed for 2 hours and 20 minutes at 50° C.±2° in a water bath. Control slides were treated just as the experimental except that no ribonuclease was added to the buffer solution. After incubation, the slides were passed through 2 changes of distilled water, and experimental and control slides were placed together in the same container and stained with Unna's carbol pyronin methyl green stain at 40° C. for 10 minutes. Later another set of control and experimental slides was incubated and stained. Incubation lasted only 2 hours, but otherwise the procedure was the same.

Pyronin methyl green stains chromatin of the resting nucleus, as well as the chromosomes, a blue-green or purple, while the red stain of the pyronin is located in the cytoplasm and the plasmosomes. Brachet (9) found that the basic dye, pyronin, often failed to stain tissue sections after ribonuclease digestion.

The control and experimental slides from the ribonuclease digestions were compared side by side with a dissecting microscope, and slides of the various organs were likewise compared for relative degree of cytoplasmic basophilia. The best that could be done by this method was to arrange the organs in a series of intensities of enzyme-preventable stain.

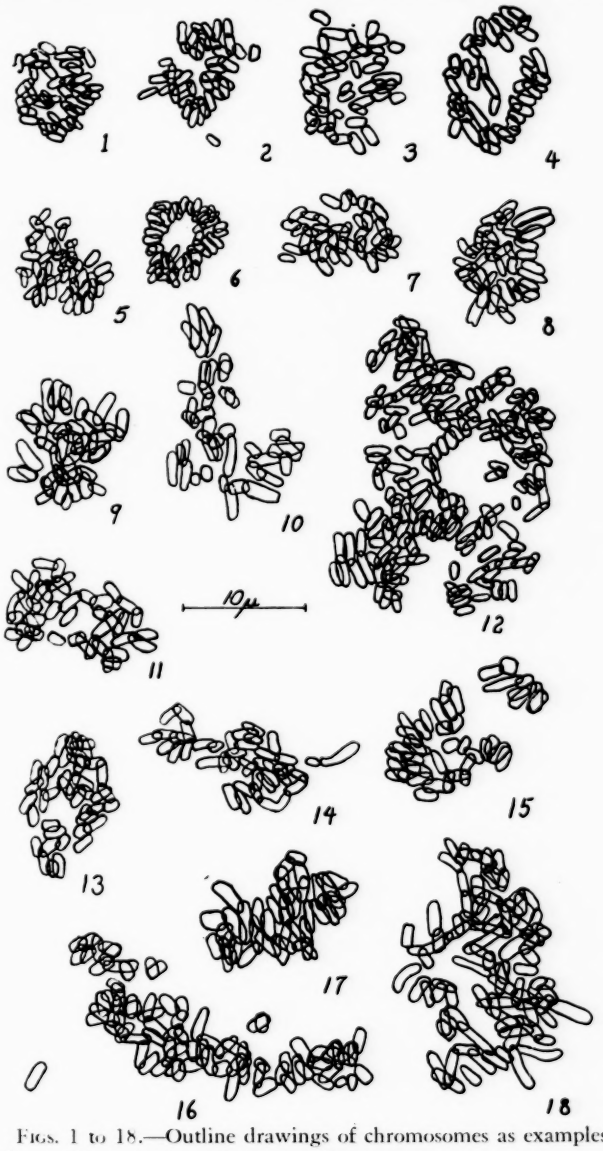
RESULTS

The results of the determinations of chromosome volume are summarized in Table I. The range of average chromosome volume that characterizes each organ is well maintained from one animal to another in the adult group, as can be seen in the kidney and liver, even in regeneration of the latter (3). Chromosome size in a given organ may be different for different stages of development. The liver and kidney chromosomes increase about one-half in average volume from the 2 day male to the adult male rat, but the chromosomes of the small intestine stay about as small in the adult as they were in the young animal. Chromosome size is more uniform in the young animal than in the adult; this suggests a still greater uniformity in the embryo. Bimodality in the frequency distribution of average chromosome volumes in the adult liver, attributed previously (3) to several cell types, is again found. The following seriation of chromosome sizes is evident in the adult animals: beginning with the spleen, small intestine (chiefly epithelium) and lung, all of which have an average chromosome volume of about 0.5 cubic micron, the average volume increases in the adrenal to 0.7, in the kidney to 0.9, and in the liver to about 1.0 cubic micron. Mitotic figures in metaphase are illustrated in outline drawings of the chromosomes in Figs. 1 to 18.

TABLE I: DISTRIBUTION OF METAPHASE FIGURES ACCORDING TO AVERAGE CHROMOSOME VOLUME

Average volume of chromosomes μ^3	Number of metaphase figures													
	Rat A						Rat D				Rat B		Rat C	
	Sm. Int.	Testis	Skin	Kidney	Liver	Spleen	Sm. Int.	Lung	Kidney	Liver	Liver	Liver	Kidney	Adrenal
0.2-0.3							1	1						
0.3-0.4	1				1	7	5	3						
0.4-0.5	10	2	1	2		9	7	6						2
0.5-0.6	8	8	9	5	3	7	5	10		1	1	1		2
0.6-0.7	4	13	12	12	9	2	6	5	5	1	5	6	4	5
0.7-0.8	1	2	2	5	7		1		4	2	5	4	7	10
0.8-0.9			1	1					6	4	3	1	3	4
0.9-1.0	1				2				1	5	2	2	6	2
1.0-1.1					1				3		3	3	3	
1.1-1.2					1				2	1	1	1	2	
1.2-1.3					1				2	2	3	3		
1.3-1.4									1	2		2		
1.4-1.5										3	1	1		
1.5-1.6										3	1			
1.6-1.7									1	1				
1.7-1.8												1		
Total No.	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Av. Vol. (μ^3)	0.55	0.61	0.63	0.64	0.72	0.46	0.50	0.51	0.93	1.12	0.93	0.96	0.85	0.72
St. Dev.	± 0.12	0.07	0.08	0.09	0.16	0.10	0.12	0.11	0.26	0.31	0.27	0.31	0.16	0.13

The difference between two means of chromosome volume may be considered statistically significant if it exceeds 3 times its standard deviation. In newborn Rat A the mean chromosome volumes of the small intestine, testis, skin, and kidney are not significantly different from one another. The small intestine and testis each differ significantly from the liver, although the kidney and skin do not. The change in average chromosome volume from Rat A to Rat D is of statistical significance for the kidney and the liver, but not for the small intestine. In Rat D, the average chromosome volumes of the spleen, lung, and small



FIGS. 1 to 18.—Outline drawings of chromosomes as examples of metaphases in normal organs of the rat.

FIG. 1.—From small intestine of 2 day old Rat A; 42 chromosomes, average volume 0.6 cubic micron; diploid.
FIG. 2.—From testis of Rat A; 41 chromosomes, average volume 0.6 cubic micron.
FIG. 3.—From skin of Rat A; 43 chromosomes, average volume 0.7 cubic micron.
FIG. 4.—From kidney of Rat A; 44 chromosomes, average volume 0.6 cubic micron.
FIG. 5.—From lung of 84 day old Rat D; 44 chromosomes, average volume 0.5 cubic micron.
FIG. 6.—From spleen of Rat D; 42 chromosomes, average volume 0.4 cubic micron.
FIG. 7.—From small intestine of Rat D; 40 chromosomes, average volume 0.5 cubic micron.
FIG. 8.—From adrenal of adult Rat C; 42 chromosomes, average volume 0.7 cubic micron.
FIG. 9.—From kidney of Rat C; 42 chromosomes, average volume 0.9 cubic micron.
FIG. 10.—From kidney of Rat D; 41 chromosomes, average volume 1.1 cubic microns.
FIG. 11.—From liver of Rat A; 37 chromosomes, average volume 0.9 cubic micron.
FIG. 12.—From liver of Rat A; 174 chromosomes, average volume 0.7 cubic micron; octoploid.
FIG. 13.—From liver of Rat C; 42 chromosomes, average volume 0.7 cubic micron.
FIG. 14.—From liver of Rat B; 40 chromosomes, average volume 0.8 cubic micron.
FIG. 15.—From liver of Rat C; 42 chromosomes, average volume 1.2 cubic micron.
FIG. 16.—From liver of Rat C; 81 chromosomes, average volume 1.3 cubic micron.
FIG. 17.—From liver of Rat D; 41 chromosomes, average volume 1.3 cubic micron.
FIG. 18.—From liver of Rat D; 84 chromosomes, average volume 1.5 cubic micron; tetraploid.

intestine are not significantly different from each other, but they do differ significantly from those of the kidney or liver. The mean chromosome volumes of the kidney and liver of Rat D differ by an amount that is between 2 and 3 times its standard deviation; and 1.02 ± 0.27 cubic micron, the mean chromosome volume of 237 metaphases of the livers of 7 adult male rats, including regenerating and control livers (3), is statistically significantly different from 0.89 ± 0.21 cubic micron, the mean chromosome volume of 50 metaphases of the kidneys of Rats C and D. The liver chromosomes of Rats B, C, and D do not differ significantly, nor do the kidney chromosomes of Rats C and D. The adrenal chromosomes of Rat C are significantly smaller than the kidney chromosomes of Rat C, on the one hand, and significantly larger than the lung chromosomes of Rat D, on the other.

The seriation of the rat organs with respect to average chromosome volume is maintained in the B vitamin assays of organs of Wistar rats made by Mitchell and Isbell (33) and Taylor, Pollack, and Williams (37); approximately similar seriations of organs were found for all the individual B vitamins studied except inositol and folic acid. It is known, or thought probable, that nicotinic acid, thiamin, riboflavin, pantothenic acid, pyridoxin, and biotin are closely related to enzymes; inositol, on the other hand, seems to be concerned structurally in phospholipid formation (8). Since chromosomes have been looked on as enzyme factories (43), inositol was not considered in drawing up the series of organs according to total B vitamin content. If the weights of thiamin, riboflavin, nicotinic acid, pantothenic acid, pyridoxin, biotin, and folic acid given by Mitchell and Isbell (33) be added together for the individual organs, the following series in descending order of vitamin concentration is obtained: liver, kidney, heart, muscle, spleen, brain, lung, in approximately the proportion of 10:6:6:3:3:3:2 respectively. From the graphs of Taylor, Pollack, and Williams (37) the descending series of vitamin concentration, again excluding inositol, may be read off: liver, kidney, heart, adrenal gland, brain, spleen, lung, muscle. Combining the 2 series and omitting the organs in which no mitoses were found, we have the master series of liver, kidney, adrenal, spleen, and lung for comparison with the chromosomal series. The total quantities of vitamins are reasonably different from one another, with the exception of the spleen and the lung. The series of organs with respect to decreasing average chromosome volume is liver, kidney, adrenal, lung, and spleen, but the values of the last 2 are not significantly different.

The total B vitamin content has also been determined for fetal rat liver (40). It is about half that of the adult liver. Since the liver chromosomes of the newborn rat are considerably smaller than those of

the adult, it may be assumed that chromosomes of the embryonic liver are likewise small and that here again there is a direct relation between chromosome size and B vitamin content of the organ.

In both incubations with ribonuclease the enzyme was effective in removing material with affinity for the basic dye, pyronin. In some tissues of which the experimental slides had more than a modicum of stain there must have been acid material other than ribonucleic acid that stained with pyronin. Ribonuclease digestion had no effect on the pyronin-staining properties of the mucin of goblet cells or of the granules in the large mast cells of the heart and lung and in the small mast cells of the villi. The stained materials in these cases are sulfuric acid esters of complex polysaccharides (14). It was found that the ribonuclease digestion had left very little of the other material, presumably ribonucleic acid, that stained with pyronin in the pancreas, the epithelium of the small intestine, the lung, and the spleen. Ribonucleic acid seemed to be concentrated in the pancreas in the cytoplasm near the nuclei of the acinus cells, and there was a little in the zymogen granules of the distal cytoplasm. In the lung ribonucleic acid was distributed in good quantity through the cytoplasm of the cells of the interalveolar septa and the epithelium of the bronchioles. In the small intestine ribonucleic acid was most concentrated in the 2 mitochondrial zones of the cells of the intestinal epithelium. In the spleen the concentration of the acid was low and variable; the cell types corresponding to the r-cells of Bryson (10), with relatively large, pale nuclei and visible plasmosomes (especially the megakaryocytes) contained more cytoplasmic ribonucleic acid than did the cell types, such as the lymphocytes, in which the nucleic acid was chiefly intranuclear and of the desoxyribose type. The liver control slides were stained about 4 times as intensely as the experimental; ribonucleic acid was found in the nucleoli and in rough masses in the cytoplasm of the hepatic cells, especially near the nuclei. The kidney sections stained perhaps one-third as heavily with pyronin after ribonuclease digestion as without the enzyme treatment; ribonucleic acid seemed to be diffusely distributed through the cytoplasm of the renal tubule cells, but the pyronin stain was very weak in the glomeruli and the endothelium of the blood vessels. In the heart ribonuclease digestion eradicated only a small part of the moderate staining capacity of the muscle cells.

The following series of organs was found in both digestion experiments in order of decreasing concentration of ribonucleic acid, *i.e.,* of stainable material removable by ribonuclease: pancreas, lung, small intestine, liver, kidney, spleen, and heart. The liver and kidney seemed to have about the same concentration of ribonucleic acid; although the total intensity of stain may have been slightly greater in the kidney, a greater proportion of stainable material was removed by ribonuclease from the liver. In view of the different species used, this series is not made improbable by the fact that Davidson and Waymouth (15) found adult sheep organs to have the following order of decreasing concentration of ribonucleic acid: testis, gut, kidney cortex, lung, spleen, liver, brain, heart, muscle, and thyroid.

The series of organs in order of decreasing average chromosome volume: liver, kidney, lung, small intestine, and spleen, is unlike that for ribonucleic acid concentration: lung, small intestine, liver, kidney, and spleen. Therefore the concentration of polynucleotides in the cytoplasm does not determine the size of chromosomes in mitosis, nor does the size of chromosomes determine the concentration of ribonucleic acid.

The data on nuclear volumes, their frequency, and the number of plasmosomes in nuclei of different volume-groups are included in Figs. 19 to 24.

The organs studied in 2 day old Rat A have essentially unimodal distributions of nuclear volumes. The average nuclear volumes are 390 cubic microns for the small intestine; 401 for the kidney; 411 for the testis; 440 for 44 epidermal nuclei and 477 for 6 dermal nuclei of the skin; and 501 for the liver, exclusive of the one nucleus of 1,220 cubic microns found. Since this large nucleus contained 12 plasmosomes, a number double the maximum found in the others, it was probably made up of a tetraploid number of chromosomes instead of the diploid number presumably in the others. Besides 24 approximately diploid metaphase figures drawn from Rat A liver, one metaphase (Fig. 12) was found with 174 chromosomes, nearly the octoploid number, 168. Evidently a small degree of polyploidy is already present in the liver of the rat soon after birth.

All 5 organs of the very young rat show 6 as the maximum number of plasmosomes, with the exception of the single presumably tetraploid nucleus of the liver. Apparently, then, there are 3 plasmosome-bearing chromosomes in the haploid set of the rat.

Like the chromosomes, the nuclei in the 2 day rat have a restricted range of size. The liver shows the largest chromosomes and also has the largest nuclei. The small intestine has not only the smallest average nuclear volume, but also the smallest average chromosome volume. To a certain degree, then, we see upheld here Jacobj's assumption (26) of a direct proportionality between nuclear and chromosomal size in different tissues of the same animal. The nuclei of these 5 organs differ with respect to amount of stainable chromatin and development of plasmosomes. The liver nuclei have the best development of chromatin and nucleoli. The nuclei of the small intestine have a plasmosomal development about equal to that of the

basal cells of the epidermis. The testis of the 2 day rat does not show the good differentiation between heavily heteropycnotic small spermatogonial nuclei and lightly-staining r-nuclei with big plasmosomes noted by Bryson (10) in the 5 day mouse testis. The smallness and frequent apparent lack of plasmosomes and heterochromatic granules in the nuclei of the 2 day rat kidney probably indicate an absence of correspondence between size of normal mitotic chromosomes and concentration of histone or ribonucleic acid, as enzymatic digestion of adult tissues also demonstrated.

Let us examine the adult organs with respect to plasmosomes and nuclear volumes. The kidney and adrenal gland of Rat C, the small intestine, kidney, lung, and spleen of Rat D show little difference from the organs of the 2 day rat in the range of volumes over which the nuclei are distributed or in the number of plasmosomes carried by the nuclei. We note that among the 50 nuclei studied in the adrenal of Rat C, one was twice as large as the others and had 12 plasmosomes, twice the maximum number exhibited by the smaller nuclei. This nucleus was probably tetraploid in number of chromosomes.

In all the adult livers, however, a peculiar situation is apparent. The mode of nuclear volumes has shifted to about twice that in the 2 day liver, but the number of plasmosomes has not increased in the nuclei of the modal volume-group. Only in the largest nuclei do the plasmosomes give evidence of chromosomal polyploidy. In the liver of Rat B the percentage of resting nuclei with more than 6 plasmosomes is 3, and the percentage of polyploid metaphase figures is 28. In Rat C these percentages are 7 and 8 per cent respectively; in Rat D, 12 and 28 per cent. In a regenerating liver on the sixth day after partial hepatectomy (3) they are 13 and 37, and in control livers they are 12 and 44. In every case the percentage of polyploid metaphase figures exceeds, or nearly equals, the percentage of resting nuclei with more than 6 plasmosomes apparent. An explanation should be sought in the tendency of plasmosomes to fuse, in the greater attraction of large equatorial plates for the eye, and in the small samples of metaphase figures. Although some of the large nuclei with 6 or fewer plasmosomes in the livers may be polyploid in chromosome number, most of them are very likely diploid. Some of the livers, such as that of Rat C, display a distinct bimodality of frequency of nuclear volumes; the nuclei clustered about the first mode, many of which are hepatic nuclei, have the same volumes as most of those in the 2 day rat liver, and those in the second group are about twice as large. Nevertheless, according to plasmosome number, the nuclei in the second group are not only diploid but also nonpolytene in their chromosomes. Probably the diploid sets of large chromosomes so common in the liver form these large resting nuclei. A beginning of the process of enlargement to a bimodal condition can be noted in the liver of the 2 day rat; there 2 nuclei of the 50, although apparently with only 4 plasmosomes each, are twice as large as the modal volume, and correspondingly, a few of the metaphases contain chromosomes averaging about 1 cubic micron. It should be pointed out that the mouse is different in this respect, since the liver nuclei regularly double in plasmosome number with progressive doublings of volume (7).

Although we have now seen some instances that tend to corroborate the concept of a direct relation between chromosome size and nuclear volume, there are contradictory instances at hand. The size of the kidney nuclei seems not to increase from 2 days to adulthood. In the kidney of young Rat A, 50 nuclei averaged 401 cubic microns; in Rat C the average was 363 and in Rat D, 405 cubic microns. Nevertheless, the average chromosome volume increased about 50 per cent from the newborn to the adult rat kidney. The nuclei in the adult kidneys give the impression, however, of having bigger plasmosomes and a slightly greater amount of stainable chromatin than do the nuclei of the young rat kidney. The adrenal nuclei of Rat C are slightly larger than the kidney nuclei and have a somewhat better development of the nucleolar apparatus, yet the chromosomes of the kidney are larger by one-fourth.

The question marks in the table of plasmosome numbers in the spleen have reference chiefly to nucleoli in lymphocytes. In the spleen the nucleic acid balance is shifted far in favor of desoxyribonucleic acid (15), and this fact is seen cytologically in the heavily chromatic lymphocytes with questionable plasmosomes, if any. It is also difficult to make out plasmosome numbers in many of the nuclei of the lung, as evidenced by dash lines in the table.

The conclusions to be drawn from our study of nuclear volumes are that, although the supposed direct relation between chromosome size and nuclear size may hold approximately within some individual cell types, it does not necessarily hold for the same cell type at different ages, nor does it necessarily hold from one cell type to another. A doubling of chromosome number, as witnessed in the resting nucleus by a doubling of the number of plasmosomes, carries with it an approximate doubling in nuclear volume. However, in normal rat tissues it cannot be said that an enlarged resting nucleus necessarily contains a greater number of chromosomes unless its plasmosomes are radically increased in number.

To summarize the results, we note that in normal rat organs the average chromosome volume is (a) directly proportional to the total concentration of B vitamins with the exception of inositol, (b) not strictly proportional to nuclear volume, (c) not proportional

NUCLEAR VOLUME IN CUBIC MICRONS	APPARENT PLASMOSOME NUMBERS IN 50 RESTING NUCLEI
RAT A LIVER	
300–350	4 6
350–400	4 5 5
400–450	1 2 3 4 4 4 4 5 5 6 6
450–500	3 3 4 5 5 5 6 6 6 6 6 6 6
500–550	4 4 4 5 5 5 6 6 6 6
550–600	1 3 4 4 5 5 5
600–650	
650–700	3
950–1000	4 4
1200–1250	12
RAT A KIDNEY	
200–250	/
250–300	5 / / / / / / / / /
300–350	3 5 / / / / / / / / / / / /
350–400	5 / /
400–450	4 4 5 / / / / /
450–500	2 2 2 3 6 / / /
500–550	5 5 /
550–600	4 5
600–650	3 5
850–900	5
RAT A SKIN	
250–300	3 5 6 6
300–350	3 3 4 4 5 6
350–400	2 3 4 4 5 5 5 5 5 5 6 6 6 6
400–450	3 3 4 4 4 5 5 6 6
450–500	3 4 4
500–550	2 4 4 6 6 6
550–600	4 4 6
600–650	
650–700	5
700–750	2 6
750–800	4
RAT A SMALL INTESTINE	
250–300	3 4 5 5
300–350	2 3 3 3 3 4 4 5 5 5 5 6
350–400	2 3 4 4 4 4 4 4 4 5 5 5 5 5 6 6 6 6 6 6
400–450	3 4 4 4 4
450–500	3 4 4 4 6
500–550	
550–600	4 6
600–650	5
RAT A TESTIS	
200–250	2 6 6
250–300	2 5 5
300–350	3 3 4 4 4 4 5 6 6 6 6
350–400	4 4 4 4 5 5 5 6
400–450	4 5 5 5 5 6 6 6 6
450–500	3 4 4 6 6 6
500–550	2 5 6
550–600	6 6 6 6
600–650	5
650–700	
700–750	1
750–800	5

FIG. 19

RAT B LIVER

NUCLEAR VOLUMES IN CUBIC MICRONS	APPARENT NUMBERS OF PLASMOSOMES IN 100 RESTING NUCLEI
100–200	5
200–300	? 3 3 4
300–400	1
400–500	1 2 2 4 5
500–600	3 5
600–700	3 3 4 4 5 5
700–800	6 6 6 6
800–900	4 5 5 5 5 5 5 6 6 6 6 6 6 6 6
900–1000	2 2 4 4 5 6 6 6 6 6 6 6 6 6 6 6 6 6
1000–1100	3 3 3 4 4 5 5 5 5 6 6 6 6 6 6 6
1100–1200	3 4 4 5 5 5 5 5 5 6 6 6 6 6 6 6
1200–1300	1 5 5 6 6 6 6
1300–1400	6 6 6
1400–1500	
1500–1600	
1600–1700	12
1700–1800	5
1800–1900	9
1900–2000	
2000–2100	
2100–2200	11
2200–2300	
2300–2400	3

FIG. 20

NUCLEAR VOLUMES IN CUBIC MICRONS	APPARENT NUMBERS OF PLASMOSOMES IN RESTING NUCLEI
RAT C LIVER, 100 NUCLEI	
100–200	2
200–300	? 2 4 5
300–400	? 1 2 3 4 4 4 6
400–500	1 1 1 2 4 4 4 4 5 5 5 6
500–600	2 3 3 4 4 4 5 5 5
600–700	3 3 5 6
700–800	4 5 5 5 5 6 6 6 6 6 6 6 6 6
800–900	5 5 6 6 6 6 6 6 6 6 6 6 6 6 7
900–1000	2 4 4 4 5 5 6 6 6 6 6 6 6 6 6 6 6 6 7
1000–1100	4 4 4 5 5 6 6 7 7 7
1100–1200	5 6 6 11
1700–1800	12
RAT C KIDNEY, 50 NUCLEI	
150–200	5
200–250	
250–300	3 3 4 5 5 5 5
300–350	1 2 2 2 2 3 3 4 4 4 6
350–400	2 2 2 3 3 3 4 4 4 4 4 4 4 4 5 5 5 5 6 6
400–450	4 4 4 4 5 6 6
450–500	2 5 6
500–550	4
RAT C ADRENAL, 50 NUCLEI	
200–250	4
250–300	3 5 5
300–350	3 3 4 4 5
350–400	2 3 5 5 6 6 6 6
400–450	3 4 4 5 6 6
450–500	3 4 4 4 4 4 5 5 5 5 5 5 5 6 6
500–550	3 3 5 5 5 5 6 6
550–600	5
600–650	4 5 6
900–950	12

FIG. 21

NUCLEAR VOLUMES IN CUBIC MICRONS	APPARENT PLASMOSOME NUMBERS IN 50 RESTING NUCLEI
RAT D LIVER	
100–200	3 5
200–300	? 4 4
300–400	1 2 3 6
400–500	3 4 5 6
500–600	1 1 3 3 5 5
600–700	3 4 4 5 5 5 5 6
700–800	2 6
800–900	4 4 6
900–1000	4 5 6 6 6 6 6 6 11
1000–1100	4 4 5 5 6 6 7
1100–1200	7
1200–1300	5
RAT D KIDNEY	
250–300	1 3 4 6
300–350	2 3 3 3 4 4 4 4 5 5 5
350–400	3 4 4 4 4 5 5 5 5 6 6
400–450	1 4 4 4 4 5 5
450–500	2 3 4 4 5 5 5 6 6 6 6 6 6
500–550	3 5 6
550–600	5
RAT D LUNG	
100–150	? ? 4 4 5 6 / / / / / / / /
150–200	? 4 6 / / / / / / / / / /
200–250	? 5 6 / / / / / / / /
250–300	4 5 6 / / / /
300–350	3 4 / / / /
RAT D SMALL INTESTINE	
250–300	2 4 5 6
300–350	2 3 4 4 5 5 5 5 5 6
350–400	2 3 4 4 4 5 5 6 6 6 6
400–450	3 4 5 5 5 5 5 5 6 6 6 6 6
450–500	3 4 4 4 4 5 5 6
500–550	3 5 6 6
RAT D SPLEEN	
100–150	? ?
150–200	? ? ? ? ? ? ? ? ? 4 5 5 5 6
200–250	? ? ? ? ? ? ? 2 6 6
250–300	? 1 2 3 3 3 4 4 4
300–350	3 5 6
350–400	1 3 4 5 5
400–450	2 3 4 5 5
450–500	4 6
600–650	6

FIG. 22

ADULT RAT REGENERATING LIVER

NUCLEAR VOLUMES IN CUBIC MICRONS	APPARENT NUMBERS OF PLASMOSOMES IN 200 RESTING NUCLEI
200–300	1 2 2 3 3 4 4 5 5
300–400	1 1 2 3 4 4 4 4 4 5
400–500	2 2 2 2 3 3 3 4 5
500–600	3 3 4 6
600–700	3 6 6
700–800	3 4 5 5 5 5 5 6 6
800–900	3 3 4 4 4 5 5 5 6 6 6 6 6
900–1000	2 3 3 4 4 4 4 4 4 4 4 5 5 5 5 5 6 6 6 6 6 6 7
1000–1100	4 4 4 4 4 4 5 5 5 5 5 6 6 6 6 6 8
1100–1200	2 2 2 3 3 3 3 3 3 3 3 3 4 4 4 4 4 5 5 5 5 5
	5 5 5 5 5 6 6 6 6
1200–1300	1 2 2 2 3 3 3 4 4 5 5 5 5 6 6 6 7
1300–1400	3 4 4 4 4 5 5 6 6
1400–1500	3 3 4 4 5 6 6 6 6 10
1500–1600	2 4 6 6 9 9 10
1600–1700	4 6 8 8 10 12 12
1700–1800	9 10 10
1800–1900	4 4 6
1900–2000	
2000–2100	4 5 9
2100–2200	5 6
2200–2300	9 9 12
2300–2400	6
2800–2900	6
2900–3000	9
3000–3100	10
3100–3200	12
3200–3300	
3300–3400	11
3400–3500	24
700–3800	10
4200–4300	24

FIG. 23

ADULT RAT CONTROLS FOR REGENERATING LIVERS

NUCLEAR VOLUMES IN CUBIC MICRONS	APPARENT NUMBERS OF PLASMOSOMES IN 400 RESTING NUCLEI
100–200	1 2 2 2 3
200–300	2 3 3 3 3 3 4 4 4 4 4 5 5 5 5 5 5
300–400	1 2 2 2 3 3 3 4 4 4 4 5 5 5 5 6 6 6
400–500	1 1 1 1 2 3 3 3 3 3 4 4 4 5 5 5 5 6
500–600	1 1 2 3 4 4 4 4 4 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6
	6 6 6 6 7
600–700	1 1 2 2 3 4 4 4 4 4 5 5 5 5 5 5 5 6 6 6 6 6 6
	6 6 6 6 6 6 6
700–800	1 1 1 2 2 2 2 2 3 3 3 3 3 3 3 4 4 4 4 4 4 4
	5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6
	6 6
800–900	2 3 3 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 4 5 5 5 5
	5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6
	6 6 6 6 6 6 7
900–1000	2 2 3 3 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5
	5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6
	6 6 6 6 6
1000–1100	2 3 3 3 3 4 4 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6
	6 6 6 8 10
1100–1200	2 2 3 3 4 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 7 8
	9 10
1200–1300	1 1 3 3 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6
	7 8 12
1300–1400	2 3 3 3 3 3 5 5 5 5 6 6 6 6 8 8 9 9 10 12
1400–1500	4 5 5 6 6 8 10 11 12
1500–1600	4 5 5 5 6 11
1600–1700	4 6 9 10 11 12 12
1700–1800	5 6 6 8 8 9 11 11 11 12
1800–1900	8 10 10
1900–2000	5 8 9 10
2000–2100	7 8
2100–2200	
2200–2300	5
2300–2400	14
2400–2500	
2500–2600	11 12 13
2600–2700	9
3100–3200	11

FIG. 24

FIGS. 19 to 24.—Distribution of nuclear volumes, and apparent numbers of plasmosomes in individual nuclei of normal rat organs.

to the concentration of cytoplasmic ribonucleic acid, and (d) not strictly proportional to the relative development of heterochromatin and plasmosomes.

DISCUSSION

Several theories have related chromosomes and size of nucleus. In 1925 it was generally assumed (30) that the individual chromosome had a typical form and size, both of which could vary in each cell type of a given species, and that Boveri's law should state that nuclear or cellular size was determined not only by number of chromosomes, since that was usually constant in a given species, but also by the variable mass of each chromosome. Belar (1), in 1928, could say of chromosome size only that it varied slightly in different cells of the same organism, and that larger cells ordinarily contained large chromosomes. Jacobj (25, 26), too, was of the opinion that cell types with larger nuclei had larger chromosomes, and in his studies on nuclear volume found certain regularities that he applied to the chromosomes. Jacobj and a number of others have presented evidence that the increase in nuclear volumes in many plant and animal tissues follows a discontinuous pattern such that the modes of nuclear volume make a geometric series of this type: 1:2:4:8. In 1935 Jacobj transferred this concept from the single organ to the whole organism, in this instance the human body (26). Taking 1 as the volume of the typical cell nucleus, such as may be found in the pancreas, Jacobj extended his geometric series downward to cover microlymphocytes and upward over spinal ganglion cells to make it 1/8:1/4:1/2:1:2:4:8:16:32. He concluded that the modal nuclear volumes of the various cell types were integral multiples of a fundamental quantity. The interpretation given was that differences in amount of chromosomal material, and certainly not hydration, accounted for the different nuclear classes. In transferring his ideas about the nucleus to the chromosomes, Jacobj decided that the latter also underwent a rhythmic volume doubling by the process now called endomitosis. Chromosomes of larger cell types were called polymers. With reference to the monomeric chromosomes of a microlymphocyte, *e.g.*, the chromosomes of the parotid gland, the nuclei of which were 4 times as large, were tetramers. Polymeric chromosomes either behaved as monomers or revealed their composite character by falling apart as separate monomeric chromosomes in certain cell types, under injurious conditions or with certain methods of fixation. To Jacobj a polyploid chromosome set was entirely equivalent to a diploid set of endopolyploid chromosomes. Geitler (17), however, thought that endomitotic nuclear volume doubling always, except in a few special cases, involved a doubling of chromosome number, while to Hertwig (21) it always, but for certain exceptions, resulted from the formation of

polymeric chromosomes, that could, however, be broken down by multiple successive divisions into sets of monomeric chromosomes in the daughter cells.

Our data on chromosome volumes are not in good agreement with the opinions of Jacobj and his school. For instance, we have roughly 3 groups of organs that in average nuclear volume bear to one another a 1:2:4 relationship well within Jacobj's standards. The lung, which has an average nuclear volume of 203 cubic microns, and the spleen, with 277, form the first group. The second group is made up of the adult kidney, small intestine, and adrenal, which have mean nuclear volumes of about 400 cubic microns. Finally many adult liver nuclei are about 1,000 cubic microns in volume. Since most of the nuclei are diploid, Jacobj's theories call for a 1:2:4 volume relationship of the chromosomes in these 3 groups. However, the lung and spleen chromosomes average about 0.5 cubic micron; the kidney chromosomes average 0.9, those of the small intestine 0.5, and those of the adrenal 0.7 cubic microns; while the chromosomes of the larger sort in the liver are about 1.2 cubic microns. Jacobj's views are not accurately validated. Instead of a discontinuous increase of chromosome volume by progressive doublings, there is a gradual and nearly continuous change of average chromosome volume when all organs studied are considered. Since these average volumes are not in a 1:2:4 relation, the chromosomes cannot be considered members of a polymeric group; that is, the larger chromosomes have not been derived by progressive doublings of all ultimate protomeres, as Jacobj (26) believed. This is true not only of Clara's chromosome strands "in der Anlage" (13), but also of definitive chromosome strands that are separated from one another by interfaces and additional space, whether visibly or not. The larger chromosomes cannot be composed of more strands than the smaller ones in the sense that cancer chromosomes are, because all sizes of diploid nuclei in the normal rat tissues seem to have a maximum of 6 plasmosomes, while the diploid set of cancer chromosomes often carries 12 (4).

Even within the same organ, the increase in average chromosome volume from 2 day to adult rat is not by 100 per cent, which would be required for any increase by Jacobj's theory of rhythmic volume doubling, but is more of the order of 50 per cent. Examples are furnished by the kidney and the liver.

In summary, then, let us say that at least in normal tissues of the rat the theory that nuclear growth by rhythmic doublings in volume is underlain by a similar doubling in chromosome volume that takes place by exact duplication of protomeres (protein molecules) and chromosome strands is inaccurate, except in the case of polyploidy, and there the doubling is in total chromosomal material, not in the volume of the individual chromosomes. Even the statement that the chromosomes present in large diploid nuclei are large and those in small diploid nuclei small is true only with exceptions. Degree of dispersion of chromosomal material in the resting nucleus must vary more with function than Jacobj (26) assumed. The larger normal rat chromosomes, it must be emphasized, are not larger by virtue of an increased number of discrete strands.

It may be conjectured that at least part of the explanation for differences in size of normal chromosomes lies in the quantity of nucleic acid in the cell, if this determines the amount of cytoplasmic ribonucleic acid that enters the nucleus to be transformed into thymonucleic acid and attached to the mitotic chromosomes. Perhaps the nucleic acid on the chromosomes could influence their apparent size by its own bulk. Mitchell (34) found that after x-ray or gamma radiation, when mitosis was inhibited, the concentration of nucleotides within the nucleus apparently failed to increase, although there was considerable increase of ribose nucleotides in the cytoplasm, probably because the synthesis of desoxyribose nucleic acid from cytoplasmic nucleotides was inhibited in the nuclei of irradiated cells. *Crepis fuliginosa* chromosomes have about one-fourth the volume of chromosomes of *C. neglecta,* even within the hybrid of the 2 species, and this is attributed by Tobgy (38) in part to an increased amount of heterochromatin and consequently greater ability to manufacture nucleic acid displayed by the chromosomes of *C. neglecta.* Caspersson and Santesson (12), noting that cancer cells possess an unusually high development of the heterochromatin and nucleoli, have found by ultraviolet absorption studies that those cells lying favorably situated with respect to nutriment have high concentrations of ribonucleic acid. Koller (27) has elaborated a theory of carcinogenesis built on upsets in nucleic acid metabolism. The writer and his associates have pointed out that degree of malignancy, frequency of repeated endomitosis as evidenced by greatly enlarged chromosomes, and concentration of ribonucleic acid seem to go hand in hand (7). In normal organs of the rat, however, the cytoplasmic concentration of ribonucleic acid indicated by the ribonuclease-pyronin method is not at all paralleled by average chromosome volume. Therefore not in normal tissues, and probably not in cancers, can it be assumed that the larger chromosomes are large because they carry disproportionately great amounts of nucleic acid on the same protein skeleton.

Likewise, in spite of the fact that not only are the chromosomes large in cancers but the system of heterochromatin and nucleoli is also well-developed, we find that in normal tissues the relative development of

heterochromatin and nucleoli is not a trustworthy indicator of mitotic chromosome size. The kidney furnishes the best example of big chromosomes accompanying small nucleoli and little heterochromatin in the resting nucleus, while the intestinal epithelium illustrates the converse. The size of the mitotic chromosomes in normal organs seems more likely to be governed by, and to be a reflection of, the development of the euchromatin.

The fairly normal distribution of average chromosome volume per metaphase about a mean distinctive for each cell type indicates a differentiation of the chromosomes that either causes or accompanies the differentiation of the rest of the cell. However, the variation of chromosome size around a mean for a given cell type may, so far as it is not a result of random errors in measurement, suggest that differences in chromosome size from one cell type to another are not absolute but are derivatives of a functional differentiation of the chromosome subject to certain conditions like the availability of proper substrate for its own autosynthesis or for synthesis of gene-products.

But how are the B vitamins concerned in this chromosomal differentiation that expresses itself morphologically in size of chromosomes?

First we may consider the possibility that the difference in size of chromosomes from one cell type to another is solely the result of a different amount of vitamins, or perhaps of nucleotides containing vitamins, held in or on the chromosomes. Such a concept as this, however, is similar to, and less likely than, the suggestion we have previously discarded, namely, that the polynucleotide ribonucleic acid, some of which may be changed to desoxyribonucleic acid and attached to the chromosomes in mitosis, determines through differences in its concentration the size of mitotic chromosomes. Furthermore, in view of the low concentrations of the known vitamins in tissues, it would seem to require the assumption of considerable quantities of additional unknown vitamins or nucleotides notably to affect the size of the chromosomes by their own volume. It is, moreover, probably true that in most tissues the greater amount of the vitamins of a cell is in the cytoplasm. Data on this subject are admittedly meager, since among normal tissues only beef heart has been examined (24). Although here the nuclei hold greater concentrations of most vitamins than does the cytoplasm, it is probable that the nuclei make up a small fraction of the total mass and at least half of the total amount of B vitamin is in the cytoplasm. While we are not certain that all the cytoplasmic vitamins stay in the cytoplasm during mitosis, probably most of them remain attached to apoenzymes, since Peter (35) has lately modified his opinion on the mutual opposition of mitosis and cell work and has admitted that once materials have been taken up by the cell they are probably put through their normal metabolic course whether the cell is in mitosis or not. Therefore much less than the total B vitamin concentration of a given tissue is probably ever connected intimately with the chromosomes. It seems hardly likely that the greater size of some normal chromosomes, like those of the liver, is due solely to a greater amount of B vitamins on the mitotic chromosomes.

A second possibility is that the larger size of chromosomes in organs containing greater quantities of B vitamins is the result of increased amounts of primary or derived gene-products still remaining attached to the chromosomes in mitosis. These gene-products could well be proteins with a high affinity for certain vitamins. According to the differentiation of the cell the chromosomes would exhibit greater or less ability to manufacture these products, which would remain within or around the chromosomes for a time governed by the rate of their possible diffusion into the nuclear sap and cytoplasm. The recent finding of Mirsky and Pollister (32) that the nucleoprotein they have isolated from the nuclei of many cell types, including liver cells, is desoxyribonucleic acid combined with protamine or histone should not render this concept of higher protein gene-products on chromosomes inacceptable, because their method of isolation involves much washing with solutions in which higher proteins are readily soluble before the desoxyribonucleoprotein is extracted.

The third and most likely possibility is that the increased size in the larger chromosomes is the result of an increase in the chromosomal nucleoprotein. The additional chromosomal material, as we have seen, has been added in small, gradual steps, not by gross doublings, and has not been cut into more strands. It is proposed that the synthetic activity of the rat chromosomes parallels both their size and the cell's concentration of B vitamins. The chromosomes either (a) use vitamins in their own synthesis, or (b) use vitamins in the synthesis of gene-products, or (c) manufacture the protein parts of enzymes that are set free in the nuclear sap and ultimately the cytoplasm and that carry the vitamins in their prosthetic groups. While all three possibilities may be true, the last seems to be the predominant determiner of vitamin concentration for reasons set forth below.

Physiological geneticists have demonstrated that enzymes and antigens may be formed under the influence of one or a number of genes (23, 43). It has been proposed that antigens may be primary or secondary gene-products (20, 22), and that antigens and enzymes may be gene-replicas, at least in their active groups, the production of which is akin to genic reduplication (20, 43). Caspersson (11) has come to

the conclusion that the euchromatin synthesizes higher proteins, while the heterochromatin produces simpler proteins like histones, that pass from the nucleoli into the cytoplasm and stimulate there the formation of ribonucleic acid and cytoplasmic proteins.

The presence of a number of enzymes in fair concentrations can be demonstrated in the nuclei of rat liver. Thus Dounce (16) has found arginase, cytochrome oxidase, esterase, lactic acid dehydrogenase, and acid and alkaline phosphatases present in liver nuclei of Wistar rats in activities approaching or exceeding their activities in whole liver. To these Lan (29) has added *d*-amino acid oxidase, uricase, and choline oxidase. Mayer and Gulick (31) have reported the isolation from calf thymus nuclei of a fraction including a protein that resembles a globulin in solubility and isoelectric point and contains sulfur. Willmer (41) has found that Gomori's histochemical method for alkaline phosphatase indicates the presence of this enzyme on the chromosomes and in the nucleoli. It may be inferred from the data of Isbell and others (24) on the presence of quantities of the various B vitamins in isolated nuclei of beef heart and mouse cancer that enzymes containing these vitamins are normally present in the nuclei.

It seems reasonable to conclude that the euchromatin elaborates the protein portion of many enzymes, which may be given off rapidly to the cytoplasm. The euchromatin, according to its development as noted in size of chromosomes, synthesizes apoenzymes in variable quantity and thus determines the bound vitamin capacity of the organ. Here we have an explanation of the point raised by L. D. Wright and others (42), when they stated that the organ and species concerned are of more importance in determining the vitamin concentration than is the diet, within reasonable limits. It is apparent that the fact of differentiation of cell types demands that the euchromatin be functionally differentiated to synthesize not only different total quantities of the protein parts of enzymes according to cell type but also different quantities of individual apoenzymes. In some cell types the manufacture of certain enzymes may be completely inhibited. Nevertheless, since all chromosomes of a given rat cell are uniformly enlarged when one is enlarged, and since a high concentration of one B vitamin usually denotes a high concentration of all the rest (39), it is probable either that the synthetic activity of all gene loci is about the same or that there are so many gene loci producing different enzymes that the over-all effects on chromosome size and concentration of B vitamins are the same as though all gene loci were equally active. We may expect that there is some limit to smallness of chromosomes in spite of further reduction of enzyme-synthesizing activity.

Additional evidence that the relation between size of chromosome and concentration of B vitamins is perhaps mediated by the quantity of enzymes produced by the former and holding the latter is furnished by the work of Greenstein and Thompson (19) and of Shack (36). They have compared the activities of a number of enzymes in fetal and adult rat livers, and have found in general an increase from the fetal to the adult liver that corresponds well with our observation of a considerable difference in size of neonatal and adult liver chromosomes. Similarly, regenerating and control adult livers have much the same enzyme "spectrum" (19), and we have seen the very close chromosomal correspondence between these two tissues (3).

SUMMARY

1. Although chromosome sizes in normal rat organs, with some exceptions, vary in general with nuclear volume, they do not form a polymeric series because the change in average chromosome volume from one tissue to another does not progress by discontinuous doublings, and because the diploid chromosome set in all the organs examined carries only the same maximum number of 6 plasmosomes.

2. The average chromosome volume does not vary in accordance with the cytoplasmic concentration of ribonucleic acid, nor in accordance with the relative development of heterochromatin and plasmosomes. Hence it is likely that the size of the mitotic chromosome is not determined by the quantity of polynucleotides it carries.

3. The average chromosome volume in normal rat organs is closely paralleled by the total concentration of B vitamins, with the exception of inositol. The following series of adult rat organs is given in the order of decreasing average volume of chromosome: liver, kidney, adrenal, lung, small intestine, spleen. The last 3 do not differ significantly. In order of decreasing concentration of B vitamins, the literature gives the series: liver, kidney, adrenal, spleen, and lung. The same relation holds for embryonic and adult rat liver.

4. It is proposed that the difference in chromosome size from one normal cell type to another in rats depends on the development of the euchromatin. The greater the development of the euchromatin, *i.e.*, the larger are the chromosomes, the greater is their synthesis of enzymes and therefore the greater is the bound vitamin capacity of the organ.

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Size and Synthetic Activity of the Chromosomes of Two Rat Neoplasms

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Chromosome size in normal rat organs is proportional to the synthetic activity of the chromosomes, as witnessed by the concentration of B vitamins (2). Presumably the vitamins combine with some of the protein parts of enzymes produced by the chromosomes. It has been noted that chromosomes of cancer cells may be larger than those of normal cells (18), frequently just double their size (1, 3, 4, 5). Yet the vitamin concentrations reported in many cancers (22) are usually considerably lower than those in normal tissues. The apparent enigma is resolved by the structural difference between chromosomes of malignant cells and those of normal cells (1, 4, 5), which is demonstrable also in rat hepatoma 31 and Walker carcinosarcoma 256.

MATERIAL AND METHODS

Transplants of hepatoma 31 from two adult male Osborne-Mendel rats and of Walker carcinosarcoma 256 from Wistar strain rats [1] were preserved in Carnoy's fixative and prepared for microscopic examination by the acetocarmine method (21). Studies of chromosome volumes in metaphase, and of plasmosome numbers and nuclear volumes, were made exactly as they were for the normal organs described in the preceding paper (2). Fifty metaphases in each transplant of hepatoma 31, and 50 metaphases in Walker carcinosarcoma 256 were drawn. Plasmosome numbers and nuclear volumes were determined for 200 resting nuclei of hepatoma 31 (100 from each transplant) and 200 resting nuclei of the carcinosarcoma.

RESULTS

The distribution of average chromosome volumes is given in Table I. In both neoplasms a few metaphases were found to have chromosomes averaging about 0.6 or 0.7 cubic micron. The great majority of the metaphases, however, had average chromosome volumes of 1.1 to 1.6 cubic microns. In addition, there were a few metaphases with relatively huge chromosomes in the range from 2.0 to 3.5 cubic microns. These had a mean volume of 2.3 cubic microns in Walker carcinosarcoma 256 and 2.6 in hepatoma 31. One transplant of hepatoma 31 seemed to have a greater proportion of small chromosomes than the other. In the hepatoma 88 per cent of the metaphases were found to have less than 64 chromosomes, *i.e.*, to be in the diploid range, since 42 is the diploid number of chromosomes in the rat (20). In Walker carcinosarcoma 256 some 60 per cent of the metaphases were in the diploid range. Metaphases with very high chromosome numbers were not en-

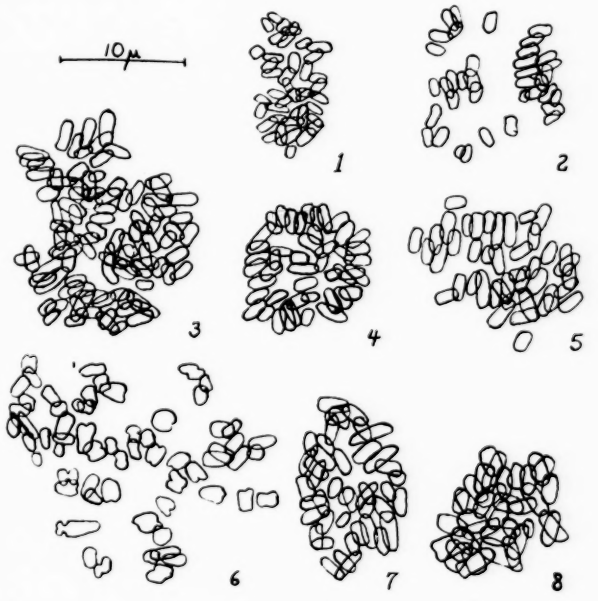
TABLE I: DISTRIBUTION OF AVERAGE CHROMOSOME VOLUMES

Average chromosome volume	Number of metaphase figures		
	Carcinosarcoma 256	Hepatoma 31	
		Rat B	Rat C
0.5-0.6 μ^3	1	2	
0.6-0.7	1	3	1
0.7-0.8	1	5	5
0.8-0.9	1	6	
0.9-1.0	4	10	2
1.0-1.1	2	6	2
1.1-1.2	6	7	6
1.2-1.3	7	2	7
1.3-1.4	8	7	5
1.4-1.5	3	1	1
1.5-1.6	7		8
1.6-1.7	2	1	2
1.7-1.8	2		1
1.8-1.9			3
1.9-2.0			1
2.0-2.1	3		1
2.1-2.2			
2.2-2.3			1
2.3-2.4			
2.4-2.5	1		
2.5-2.6			
2.6-2.7			2
2.7-2.8	1		
3.3-3.4			1
3.4-3.5			1
Totals	50	50	50
Mean group volumes:	0.65, 1.32, 2.25	0.69, 1.12	0.75, 1.38, 2.64 μ^3

* Fellow of The International Cancer Research Foundation.

[1] I am indebted to Drs. A. J. Dalton and J. W. Thompson, of the National Cancer Institute, for the Osborne-Mendel rats bearing hepatoma 31: and to Dr. Alfred Taylor, of the Biochemical Institute, The University of Texas, for the specimens of Walker carcinosarcoma 256.

countered in either growth. One prometaphase figure of Walker rat carcinosarcoma 256 was found to have 121 chromosomes, but this number is only hypertetraploid. Abortive mitoses, in which the chromosomes lay in their condensed metaphasic condition scattered throughout the cell, were to be seen in both tumors, and in them the chromosomes were either of double or about quadruple size. Figs. 1 to 17 are outline drawings of chromosome sets in or near metaphase, taken from both neoplasms.



FIGS. 1-8

FIGS. 1 to 8.—Representative outline drawings of chromosomes in metaphase in hepatoma 31.

FIG. 1.—Chromosome number 42, average volume 0.6 cubic micron.

FIG. 2.—Chromosome number 38, average volume 0.8 cubic micron.

FIG. 3.—Chromosome number 96, average volume 1.0 cubic micron.

FIG. 4.—Chromosome number 46, average volume 1.1 cubic microns.

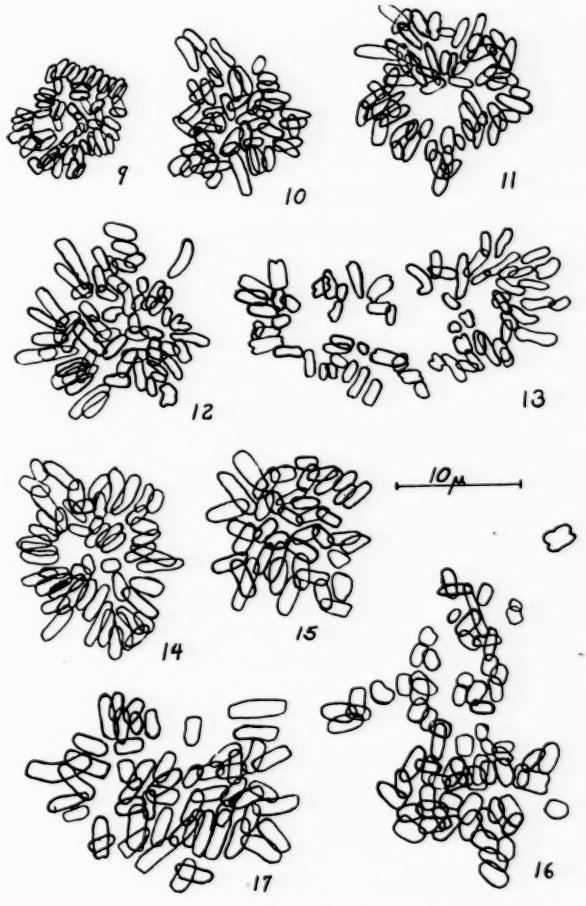
FIG. 5.—Chromosome number 42, average volume 1.2 cubic microns.

FIG. 6.—Possibly an abortive mitosis; chromosome number 63, average volume 1.3 cubic microns.

FIG. 7.—Chromosome number 44, average volume 1.5 cubic microns.

FIG. 8.—Chromosome number 38, average volume 2.7 cubic microns.

The frequencies of nuclear volumes in steps of 100 cubic microns and the frequencies of various apparent numbers of plasmosomes in the nuclei are presented in Figs. 18 and 19. The hepatoma and the carcinosarcoma are very similar in these respects. The small nuclei clustered about 500 cubic microns have plasmosome numbers that are predominantly 6 or less. Numbers up to the double of these are most common in nuclei of the volume range from 700 to about 2,000 cubic microns. Nuclei in this group also constitute the most numerous group in the neoplasms.



FIGS. 9-17

FIGS. 9 to 17.—Representative outline drawings of chromosomes in metaphase in Walker carcinosarcoma 256.

FIG. 9.—From among stroma cells; chromosome number 55, average volume 0.7 cubic micron.

FIG. 10.—Chromosome number 49, average volume 1.2 cubic microns.

FIG. 11.—Chromosome number 61, average volume 1.3 cubic microns.

FIG. 12.—Chromosome number 61, average volume 1.4 cubic microns.

FIG. 13.—Chromosome number 68, average volume 1.4 cubic microns.

FIG. 14.—Chromosome number 52, average volume 1.5 cubic microns.

FIG. 15.—Chromosome number 40, average volume 2.1 cubic microns.

FIG. 16.—Abortive mitosis; chromosome number 75, average volume 2.4 cubic microns.

FIG. 17.—Chromosome number 54, average volume 2.7 cubic microns.

While there are a few nuclei with about 20 plasmosomes at 1,500 cubic microns in the hepatoma and at 1,700 in the carcinosarcoma, they are most common in the volume range from 2,000 to about 4,000 cubic microns. A few very large nuclei were found to

contain over 24 plasmosomes, up to 36 plasmosomes in Walker 256 and to 39 in hepatoma 31; the 5 such nuclei observed in the carcinosarcoma ranged from about 3,000 to about 6,000 cubic microns, while the 3 noted in hepatoma 31 were from 2,100 to 8,100 cubic microns in volume.

It is instructive to compare Figs. 18 and 19 with the similar tabulations for normal organs in the preceding paper (2). While the distributions of nuclear volume are fairly similar in the cancers and adult liver the doubling of plasmosome numbers in the cancer nuclei, when compared to nuclei of the same volume classes in the liver, is very striking. This

HEPATOMA 31, RATS B AND C.

NUCLEAR VOLUMES IN CUBIC MICRONS	APPARENT PLASMOSOME NUMBERS IN 200 RESTING NUCLEI, 100 FROM EACH RAT
100–200	4
200–300	4 5
300–400	3 4 5 5
400–500	3 4 4 4 5 5 5 6
500–600	2 2 4 5 5 6 12
600–700	4
700–800	4 4 6 7 8 9 10 11 12
800–900	6 6 8 8 8 8 9
900–1000	1 4 5 6 7 8 8 8 9 9 9 9 10 11 11 11 11 11 12 12 12
1000–1100	4 5 6 8 8 8 8 9 10 11 11 11 11 11 12 12 15
1100–1200	4 4 6 7 8 8 9 9 9 9 10 11 11 11
1200–1300	6 6 7 7 8 8 9 9 9 9 9 9 11 11 11 11 12 12 12 12 13
1300–1400	5 6 6 7 7 7 8 8 8 8 8 10 10 10 10 11 11 13
1400–1500	5 7 8 8 9 10 10 11 11 12 12 14 20
1500–1600	3 6 7 8 9 10 10 11 11 12 12 12 16 18
1600–1700	3 9 10 12 19
1700–1800	9 11 12 16
1800–1900	10 11 11 12 15
1900–2000	10 11 11 12 12 13 14 17
2000–2100	6 9 10 10 33
2100–2200	3 16
2200–2300	12 13 15
2300–2400	
2400–2500	12 13
2500–2600	
2600–2700	15
2700–2800	
2800–2900	
2900–3000	16
3000–3100	
3100–3200	16
3200–3300	18
3300–3400	
3400–3500	16
4100–4200	18
7700–7800	39
8100–8200	32

Fig. 18

WALKER RAT CARCINOSARCOMA 256.

NUCLEAR VOLUMES IN CUBIC MICRONS	APPARENT PLASMOSOME NUMBERS IN 200 RESTING NUCLEI
200–300	5 5 6
300–400	3 5 5 6
400–500	6
500–600	5 6 6 8 12
600–700	2 4 6 7 7 7 7 10 10
700–800	5 8 10 11
800–900	4 5 5 6 6 6 7 9 14
900–1000	5 6 6 6 6 7 7 8 9 9 9 9 9 9 10 10 10 10 11 12 13
1000–1100	8 9 10 10 10 11 11 12 12 12
1100–1200	4 5 5 5 5 6 6 8 8 8 9 10 10 10 11 11 12 13 15
1200–1300	10 10 10 11 12 12 12 12 12 12 13 13
1300–1400	6 7 10 10 10 11 11 11 11 11 12 12 12 12 13 13 14
1400–1500	6 6 11 12 12 12 14 14
1500–1600	8 9 9 10 11 11 11 12 12 16 16 16
1600–1700	8 9 9 10 11 11 11 12 12 12 13 13 13 14 16 22
1700–1800	9 11 11 11 11 11 11 12 14 15
1800–1900	8 8 10 12 12 14 19
1900–2000	9 11 12 14 14 14 15 17 18
2000–2100	6 12 13 15 15
2100–2200	12 13 15 19
2200–2300	18
2300–2400	14 16 17
2400–2500	21
2500–2600	11
2600–2700	18
2700–2800	20
2800–2900	
2900–3000	32
3000–3100	16
3100–3200	
3200–3300	
3300–3400	
3400–3500	25
3500–3600	34
3600–3700	
3700–3800	22
3800–3900	
3900–4000	
4000–4100	36
6000–6100	28

Fig. 19

Figs. 18 and 19.—Distribution of nuclear volumes and apparent numbers of plasmosomes in individual nuclei of the two rat tumors employed.

doubling fails to hold only in the group of small nuclei in the cancers. Most of the doubling of apparent plasmosome numbers in the neoplastic nuclei cannot be attributed to doubling of chromosome numbers. In hepatoma 31, 12 per cent of the metaphases had over 63 chromosomes, *i.e.,* were above the diploid range, while 38 per cent of the resting nuclei seemed to have more than 9 plasmosomes and 76 per cent had over 6 plasmosomes. Six is the number of plasmosomes initially formed by the diploid set of chromosomes in normal rat organs (2). Although 40 per cent of the metaphases in the carcinosarcoma had over 63 chromosomes, 65 per cent of the resting nuclei had over 9, and in 82 per cent of the nuclei more than 6 plasmosomes could be discerned. In other words, in both neoplasms there was found a greater proportion of resting nuclei that seemed to give evidence of chromosomal polyploidy through high numbers of plasmosomes than of metaphase figures that were polyploid. The reverse is true in normal organs (2). The conclusion to be drawn is that in cancers of rats, just as in cancers of man (4), mouse (5), and goldfish (1), the chromosomes of most of the cells are individually double structures, at least in the nucleolus forming regions and probably elsewhere as well. Hence the polyploidy indicated by the high plasmosome number is in most cases an endopolyploidy of chromosomes with reduplicated but incompletely separated chromonemata. Because of the large size of the chromosomes in certain sets, it is likely that some of the cancer chromosomes are quadruple structures. The smallness of other chromosomes, and the low plasmosome numbers in the nuclei that they seem to form, are indications that these small chromosomes have the same structural complexity as the chromosomes of nonmalignant cells. That some of the small-chromosome metaphases are in stroma cells is likely, at least in carcinosarcoma 256, for in this tumor the metaphases with small chromosomes, such as those in Fig. 9, were among groups of small-nucleate cells that tended to cling together in the preparation of slides rather than to separate readily as did the obviously neoplastic cells.

DISCUSSION

Most chromosomes of hepatoma 31 and Walker carcinosarcoma 256 are about twice as large as neonatal chromosomes and the chromosomes of adult tissues with low B vitamin content (2). It is also evident that the diploid set of cancer chromosomes carries twice as many plasmosomes as does the diploid set of chromosomes in any normal rat organ studied. Therefore we must conclude that most of the chromosomes in these two rat neoplasms are double structures, if the chromosomes of a normal organ are held to be single structures. Most of the cancer chromosomes have twice the complexity of normal somatic chromosomes; *i.e.*, they must have twice as many strands, which are often separated far enough to form plasmosomes independently of one another in the same region of sister strands, as have chromosomes of normal organs, whether the latter be small chromosomes of the lung or large chromosomes of the liver.

Although the large chromosomes of the adult rat liver have about the same average volume as have most chromosomes in the two neoplasms, the equality of volume is not the result of identical causes in the liver and the tumors. In the latter the largeness of the chromosomes seems to be brought about by a reduplication of very nearly the whole structure, perhaps by an endomitosis without a division of the centromere (5), while in the liver the large size seems to result from a sort of functional hypertrophy related to the activity of the chromosomes in synthesizing gene-products (2). The liver chromosomes, in other words, are so differentiated that they manufacture great quantities of gene-products, perhaps the protein parts of certain enzymes, and to do this either the individual gene or the region about it becomes larger, whether by accretion of molecules or parts of molecules similar or dissimilar to the genic molecule or molecules we do not know. At least the liver chromosome has not undergone a reduplication of strands in the sense that the cancer chromosome has, because a set of the large chromosomes in the liver bears only half as many plasmosomes as a set of the same size in the tumors.

The preceding paper (2) has made probable a direct proportionality between average chromosome volume and synthetic activity of the euchromatin in normal rat organs. When this relation is applied to the chromosomes of the two rat tumors, the double structure of the representative cancer chromosome demands that only one-half the average volume be used in assessing the relative synthetic activity of the euchromatin. One-half the average chromosome volume in the cancers is about 0.5 to 0.8 cubic micron. Accordingly, the enzyme-synthesizing activity of the cancer chromosomes is probably of the order of that of chromosomes of newborn and possibly late-embryonic rats, or of the chromosomes of such organs as the lung, spleen, small intestine, or adrenal of the adult rat. At least for the hepatoma, which arose from liver cells, this represents a decided decrease from the activity of the chromosomes in the normal tissue of origin.

The expectation of moderate or low synthetic activity of the euchromatin in rat cancers derived from the half-volume of the chromosome is corroborated by chemical evidence. The activities or concentrations of enzymes and components of their prosthetic groups, such as the B vitamins and certain metals, have been determined in a number of neoplasms. To state that all changes in enzyme activities and metal or B vitamin concentrations in cancers, or in tissues undergoing carcinogenesis, are the results only of changes in the synthetic activity of the euchromatin is undoubtedly too ambitious a generalization to make at the present time. It has not been disproved that carcinogens affect the active enzyme molecule proper, or that the synthesis, autocatalytically or otherwise, of the protein parts of the enzymes concerned may occur in the cytoplasm. Nevertheless, the demonstration of a direct relation between average chromosome volume and B vitamin concentration in normal rat organs, supplemented by demonstration of the same relation to overall synthetic activity (2), does indicate intimate chromosomal control of the synthesis.

Many of the enzymes listed by Greenstein (12) that have been studied in rat hepatomas have an activity less than that in adult liver. Shack (24) suggested that some of the lowering in activity of *d*-amino acid oxidase in hepatoma 31 might result from an insufficient amount of the protein part of the enzyme, and a similar interpretation was given to the low activity of this same enzyme, as well as of uricase and choline oxidase, in hepatoma 31 nuclei and whole tissue by Lan (17). This investigator also found that no activity of these three enzymes was evident in Walker carcinosarcoma 256; interpretation is difficult because the normal organ from which the cancer arose is not known. Dickens and Weil-Malherbe (10) have pointed out that not only are the activities of many enzyme systems common to most tissues reduced in hepatomas, but also some special enzymatic functions of the liver are lost in the neoplastic change, part of which they consider to be of the nature of a dedifferentiation.

The B vitamin content of Walker carcinosarcoma 256 and of several rat hepatomas induced by *p*-dimethylaminoazobenzene has been found to be a fourth to a half of the B vitamin content of a number of normal rat organs (22). Greenstein (12) has summarized reports of considerable deficiencies in riboflavin and coenzyme I in rat hepatomas as compared to normal

livers. Until more data are forthcoming on the concentrations of the B vitamins in isolated nuclei of normal mouse organs, it is impossible to know how much of a decrease from normal is represented by the low B vitamin content of nuclei of a mammary carcinoma of the mouse reported by Isbell and others (15).

Certain metals associated with enzyme systems or present in the prosthetic groups of proteins have been found in decreased concentration in many neoplasms. Prominent among these are iron and calcium. Iron combines with porphyrin rings to form part of or all the prosthetic groups of catalase, peroxidase, the cytochromes, and hemoglobin, which are notoriously lowered in tumor tissue (12). Iron has been shown to decrease in mouse skin made hyperplastic under paintings with methylcholanthrene in benzene (6), and the same is now known to be true for calcium in mouse skin undergoing methylcholanthrene-induced hyperplasia and in skin carcinomas derived from such treatment, according to Carruthers and Suntzeff (7). Scott (23) has found from microincineration studies that the concentration together of magnesium and calcium in skin tumors is reduced below that in normal skin. Although magnesium normally forms the connection between the protein of yeast carboxylase and diphosphothiamin, it can be replaced by calcium as well as by several other divalent metals (11). Probably calcium plays similar cementing roles in other proteins or enzymes. Finally, the copper content of several hepatomas has been found to be lower than that of normal livers (12).

The size of the chromosomes in a rat tissue is probably an indication only of their total synthetic activity. Like the total B vitamin content of an organ, the size of the chromosome expresses a summation and does not *a priori* apply to any given enzyme. The small half-size of the average chromosome in the two rat tumors studied denotes a low over-all synthetic activity of the euchromatin, but without other information it does not exclude a high rate of synthesis of any particular enzyme. The rate of synthesis of some gene-products may very well be increased in the changed cancer chromosomes. The chromosomal change in carcinogenesis could perhaps affect the activity of different genes in different ways, depending on the past differentiation of the cell and the strain of the animal, although the metabolic similarity (10) and vitamin uniformity (22) in cancers of different origins imply changes in the same direction in the activities of many homologous genes. It is also conceivable that the multiple structure of cancer chromosomes has a phenotypic effect in the individual cell akin to that of polyploidy (5). When a cell becomes neoplastic the activity of a given enzyme system may increase, decrease, or remain constant (12); changes in individual B vitamin concentrations need not all be downward—witness biotin in rabbit skin (25); and methylcholanthrene-induced hyperplasia of mouse epidermis does not appear to cause decreases in sodium, potassium, or magnesium (6).

The heterochromatic sections of cancer chromosomes seem to be very active in the synthesis of histones and ribonucleic acid, according to Caspersson and Santesson (8) and to Koller (16). Perhaps the excessive development of the heterochromatin accounts for part of the large volume of cancer chromosomes, although the lack of correlation in normal rat organs between average chromosome volume and cytoplasmic concentration of ribonucleic acid (2) means either that the large size of cancer chromosomes is not to be so explained, or that in chromosomes of normal tissues the development of the euchromatin so far overshadows the development of the heterochromatin as to mask the effects of the development of the heterochromatin on the size of chromosomes in metaphase.

On the whole, the euchromatin of tumor chromosomes seems to be less concerned in the synthesis of gene-products, and more concerned in the synthesis of additional whole chromosomes or chromosome strands. It should be noted that physiological geneticists have looked on these two syntheses as being much the same (26, 14); therefore they may be mutually antagonistic. Perhaps the doubling of the strands in chromosomes of cancers is associated with this changed outlook in the synthetic activity of the chromosomes.

Another aspect of the chromosomal change from normal to cancerous tissues is worthy of note. Both the chromosomal and the metabolic changes in cancer can be viewed in the sense of a return to a more primitive condition, which, however, is complicated in the chromosomes by their multiple-strandedness. Except for this multiple structure the chromosomes of the two rat neoplasms studied are more like the chromosomes of newborn, or perhaps embryonic, rats than they are like those of adult organs rich in B vitamins or with high enzymatic activity. The resemblance extends to the manufacture of chromosomal products. Nucleic acid, for instance, is richer in embryonic tissues (9) and hepatomas (19) than in normal adult organs. Dickens and Weil-Malherbe (10) have interpreted the metabolic changes from normal liver and skin to hepatomas and epidermal carcinomas as a reversion to a more primitive metabolism. Greenstein and Thompson (13) found a close parallel between fetal liver and hepatomas in their enzymatic differences from adult liver; both hepatoma 31 and fetal liver were low in activity of arginase, catalase, xanthine dehydrogenase, urea-synthetic systems, cystine oxidase, cytochrome oxidase, and *d*-amino acid oxidase; the hepa-

toma and embryonic liver were higher than adult liver in activities of acid and alkaline phosphatases; and the fetal, adult, and neoplastic livers agreed in activities of ribonucleodepolymerase, desoxyribonucleodepolymerase, and amylase. West and Woglom (25) found that in several rat, mouse, and rabbit organs the biotin content was changed in the same direction from the adult in the embryonic and the neoplastic tissues: in most of the cases, as in the rat liver, the adult organ had the highest biotin content. In so far as the changes in enzymatic activity or vitamin concentration given above reflect changed synthetic activity of the chromosomes, it can be said that cancer chromosomes resemble the chromosomes of embryonic tissues in synthetic activity as well as in unit structural size (to judge from neonatal chromosomes), although the latter is obscured by the twinning process through which the cancer chromosomes have passed.

A better summarizing generalization to make is that in the shift to cancer the chromosomes of the cells involved assumed a different synthetic activity and a correspondingly different size of fundamental structural unit, besides undergoing a doubling of structure; in at least one of and perhaps in both the cancers studied the change in synthetic activity and concomitantly in size of structural unit seems to have been a decrease toward or even beyond that characteristic of the condition in the fetal or newborn animal.

SUMMARY

1. The metaphase figures in transplants of rat hepatoma 31 and Walker carcinosarcoma 256 fall into 3 classes: those with chromosomes of about the size found in normal organs poor in B vitamins, those with chromosomes twice as large, and those with chromosomes about 4 times as large. Chromosomes of double size are in the majority.

2. The proportion of division figures that are polyploid is greatly exceeded by the proportion of resting nuclei with more plasmosomes than are carried by the diploid set of chromosomes in normal organs. Therefore the chromosomes of double and quadruple size in the two neoplasms are probably composed of more discrete strands than is true in normal tissues.

3. Although the chromosomes of hepatoma 31 and normal adult liver are of about the same large size, the largeness of the adult liver chromosomes apparently expresses a functional differentiation related to great synthetic activity, while that of the hepatoma results from a twinning process. The hepatoma chromosomes are double the size of newborn or perhaps fetal rat liver chromosomes, rather than double the volume of actively functioning adult liver chromosomes.

4. The double nature of the tumor chromosomes requires that one-half their average volume be used to assess their synthetic activity. On this basis the two neoplasms used should have a low rate of synthesis of chromosomal products. This is made probable by evidence from the literature of low B vitamin content, low activity of a number of enzymes, and a decrease in certain metals in cancers.

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Comparative Glycolytic and Respiratory Metabolism of Homologous Normal, Benign, and Malignant Rabbit Tissues

With Particular Reference to the Benign Virus Papilloma (Shope) and a Transplanted Cancer Derived Therefrom (the V2 Carcinoma)

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To learn more about the changes that take place when benign tumor cells become malignant, and whether the malignant cells possess an altered metabolism, we have undertaken a comparative study of certain rabbit tumors and tissues of homologous sorts. Special attention has been given to the benign epidermal papillomas caused by the Shope virus (24), and to the V2 carcinoma—a squamous cell cancer derived originally from the cells of a Shope virus papilloma, and maintained for several years by transplantation (15). Normal and hyperplastic skin have also been studied, as well as autochthonous squamous cell carcinomas originating in virus papillomas (19), and a second transplanted epidermoid cancer—the Brown-Pearce carcinoma, which arose at the site of an old syphilitic lesion (3, 17). In addition to these epidermoid tissues, the observations have been extended to a virus-induced fibroma (23), and to a transplanted sarcoma (sarcoma I of Andrewes and Ahlström) that arose in voluntary muscle where tar and the fibroma virus had both been present (1). Values for anaerobic and aerobic glycolysis, respiratory quotient, oxygen consumption, and certain derived quotients were determined in glucose-bicarbonate medium by standard methods (8), and for oxygen consumption response to added succinate and paraphenylenediamine (9, 18, 22) when the tissues were in glucose-phosphate medium.

As bearing upon the interpretation of the metabolic findings, particular attention has been given to a histologic analysis of the materials actually employed in the manometric experiments. Sections were made of the tissue slices after the metabolic measurements had been made on them, as well as of representative slices taken before measurement. Though the tissues were all carefully selected, microscopic examination showed that cells of the types sought for study often made up only half or less of the bulk of the slices put into the Warburg vessels. For example, normal skin, and skin rendered hyperplastic by 3 or 4 applications of turpentine-acetone mixture (11), when carefully shaved from a stretched surface in a layer about 0.1 mm. thick, still provided slices that contained only a small proportion of epidermal cells (5 to 25 per cent), the rest being derma that could not feasibly be trimmed away. The "healthiest" parts of the primary carcinoma likewise contained only a rather small proportion of neoplastic cells, edematous stroma comprising the bulk; and slices of these primary tumors were, in addition, usually pultaceous in spots from bacterial infection. The benign virus papilloma and the transplanted V2 carcinoma, on the other hand, provided much more suitable materials. By taking only the basal portion of young, vigorously proliferating papillomas, slices could be procured that contained about 70 to 80 per cent or more of living papilloma cells, along with some 25 to 15 per cent or less of keratinized papilloma cells and a small proportion of derma. Furthermore, the metabolism of the keratinized cells as such could be studied by slicing separately the upper half of papillomas 4 to 6 mm. high; such slices contained about 90 per cent or more of dead squames and 10 per cent or less of living papilloma cells. The V2 carcinoma provided slices composed at best of some 40 to 60 per cent of "healthy" carcinoma cells, the rest being edematous stroma containing immature fibrocytes and occasionally infiltrated with wandering cells, chiefly lymphocytes. To evaluate the metabolism of this stroma, slices were selected for test that were composed mainly of it, with only some 15

* With the technical assistance of Marie L. Hesselbach and Doris F. MacNeary.

to 30 per cent of carcinoma cells. Additional studies were made with the benign virus-induced fibroma, which though quite different in microscopic appearance from the V2 stroma, is also an edematous tissue containing proliferating fibroblasts that often appear "sick"; it regularly regresses (23), and is not neoplastic in a strict sense.

EXPERIMENTAL RESULTS

Metabolism of malignant, benign, and normal rabbit tissues in bicarbonate medium.—Table I provides a summary of the glycolytic and respiratory estimations. The V2 carcinoma slices having 40 to 60 per cent of malignant cells yielded by our technic anaerobic glycolysis values ($Q^{N_2}{}_A$) averaging 10.2, and aerobic glycolysis values ($Q^{O_2}{}_A$) averaging 4.6. The $Q^{N_2}{}_A$ values for the Brown-Pearce carcinoma (average 11.8) were slightly greater than those for the V2 carcinoma, and so, too, were those for the rabbit sarcoma I of Andrewes and Ahlström (average 12.0). The average $Q^{N_2}{}_A$ value obtained with V2 carcinoma slices containing a preponderance of stroma was relatively low (6.3), and that for the virus-induced fibromas was notably so (2.9).

The papilloma slices having 70 to 85 per cent of living cells gave average anaerobic and aerobic glycolysis values of 6.9 and 2.8 respectively. These values, it will be observed, are significantly lower than the corresponding average values for the V2 carcinoma, as statistical analysis confirms. It is noteworthy, moreover, that the papilloma slices contained a greater percentage of neoplastic cells than did the V2 carcinoma slices (second column of Table I) and that the observed differences in the metabolism of the two tissues become even greater if allowance is made for this factor. In this connection, the benign papilloma of the wild cottontail rabbit gave metabolic values indistinguishable from those of the domestic rabbit growth, whereas the keratinized papilloma, which provided slices containing 10 per cent or less of living cells, gave negligible $Q^{N_2}{}_A$ values.

The findings with the skin and primary carcinoma tissues are included, but owing to the small proportion of epidermal cells present in the slices and to the bacterial infection of the carcinomas it is difficult to make a close quantitative comparison between these tissues and the Shope virus papilloma or the transplanted malignant tumors. It will be noted that the skin slices provided $Q^{N_2}{}_A$ and $Q^{O_2}{}_A$ values considerably lower than those for the papilloma slices, but the differences may have been due to the much lower proportion of epidermal cells present in them. In this connection, Berenblum, Chain, and Heatley (2), who used a special technic for slicing and nucleic acid-phosphorus content instead of dry weight for comparison, reported no difference between the glycolyzing capacity of normal rabbit skin and of benign papillomas induced with the Shope virus. The cellular composition of their materials was not described, however, and hence comparisons on a basis of content of homologous epidermal cells cannot be made. It has been indicated elsewhere (6, 10) that they did not extend their studies to homologous malignant tumors, which, as our findings show, differ significantly in glycolyzing capacity from the benign papilloma.

Further information is provided by the derived metabolic quotients (Table I), which relate glycolysis to oxygen consumption independently of dry weight, although it is to be noted that certain of the quotients are calculated from comparatively few determinations. The V2 carcinoma yielded a positive fermentation excess, an extent quotient above zero, and Myerhof oxidation quotient several times unity, in which respects it may be considered characteristically "malignant" within the limitations of these criteria (4-6). The Shope virus papilloma cells provided a fermentation excess quotient of approximately zero, and an extent quotient of about 6.0, in addition to intermediate glycolysis rates. The quotients given by the skin slices indicate a difference between this tissue and the benign papilloma that is not brought out by a consideration of the glycolysis values alone. In our experiments the Meyerhof oxidation quotient for skin was less than unity, the fermentation excess was negative, and the extent quotient was only half as great as that for the papilloma. Values for the two latter quotients that similarly differentiate the normal skin and the benign papilloma may be calculated from the data of Berenblum, Chain, and Heatley already mentioned, even though their values for anaerobic glycolysis failed to distinguish between the two tissues. In passing it is interesting to note that the extent quotient for the virus-induced fibroma is very high (14.5), suggestive of "malignancy," but its low $Q^{N_2}{}_A$ and Q_{O_2} values preclude this characterization (4-6).

The respiratory quotients of the tissues (skin, hyperplastic skin, fibroma, papilloma, and V2 carcinoma) were all below unity. Previous observations have pointed to the lack of distinction in this regard between the generality of tumors and the majority of adult tissues (4-6, 10).

It is noteworthy that the per cent dry weight of the tissues varied from 10.5 in the case of the fibroma to 24.0 in the case of normal skin, and that certain of the differences, notably that between the V2 carcinoma (dry weight = 12.9 per cent) and the virus papilloma (dry weight = 17.9 per cent), are decreased if the Q values are calculated on the basis of wet weight.

TABLE I: COMPARATIVE GLYCOLYTIC AND RESPIRATORY METABOLISM OF NORMAL, BENIGN, AND MALIGNANT RABBIT TISSUES IN BICARBONATE MEDIUM

TABLE I: COMPARATIVE GLYCOLYTIC AND RESPIRATORY METABOLISM OF NORMAL, BENIGN, AND MALIGNANT RABBIT TISSUES IN BICARBONATE MEDIUM

Tissue	Histological analysis of tissue slices employed	Per cent dry weight	Anaerobic glycolysis $Q_A^{N_2}$	Aerobic glycolysis $Q_A^{O_2}$	Respiratory quotient R.Q.	Oxygen consumption Q_{O_2}	Extent quotient $3Q_A^{N_2}/Q_{O_2}$	Fermentation excess, U $Q_A^{N_2}-2Q_{O_2}$	Meyerhof oxidation quotient, M.O.Q. $3(Q_A^{N_2}-Q_{O_2}^A)/Q_{O_2}$
Transplanted V2 carcinoma derived † from the Shope virus papilloma (15); 32nd and 34th transfers (10-20 days)	About 40-60% carcinoma cells; remainder edematous stroma, composed mainly of fibrocytes, usually infiltrated scantily with wandering cells, chiefly lymphocytes	12.9^{13}_{13}	10.2^{19}_{10} *	4.6^{4}_{2}	0.67^{2}	3.2^{6}_{3}	9.5	3.6	5.1
Brown-Pearce carcinoma (20 days) (3)	About 65% malignant cells; remainder muscle and necrotic tumor cells, lymphocytic infiltration scanty	15.4^{2}_{2}	11.8^{4}_{2}						
Andrewes-Ahlström sarcoma (R.S.I.) (20 days) (1)	About 55% malignant cells; remainder muscle and necrotic tumor cells, lymphocytic infiltration scanty	14.3^{2}_{2}	12.0^{6}_{2}						
Benign Shope virus papilloma (domestic rabbit, 3-32 wks.) (24)	About 70-85% living papilloma cells; 10-20% keratinized papilloma cells; remainder derma	17.9^{13}_{13}	6.9^{27}_{13} *	2.8^{2}_{2}	0.84^{1}	3.0^{1}_{1}	6.9	+0.9	4.1
Benign Shope virus papilloma (wild cottontail rabbit, 4 wks.) (24)	Similar to domestic rabbit papilloma	19.9^{8}_{8}	6.9^{8}_{4}						
Keratinized papilloma (upper half of growths; 0.4-0.6 cm. tall)	0-10% living papilloma cells; remainder mostly dead squames	20.9^{3}_{3}	0.5^{7}_{3}						
V2 carcinoma as above, but selected so that bulk of tissue was stroma	About 15-30% V2 cells; remainder stroma	11.5^{8}_{8}	6.3^{8}_{4}						
Virus-induced fibroma (6-13 days) (23)	Edematous, collagenous tissue containing fibroblasts, usually infiltrated moderately with wandering cells, both polymorphonuclear leukocytes and lymphocytes	10.5^{6}_{6}	2.9^{11}_{8}	1.3^{2}_{1}	0.92^{1}	0.6^{2}_{1}	(14.5)	(+1.7)	(8)
Primary carcinomas originating in 32 wks. old Shope virus papilloma (19)	About 20-30% squamous carcinoma cells amidst myxomatous stroma	13.0^{4}_{4}	5.0^{8}_{4}						
Normal skin (ear, belly)	About 5-15% normal epidermal cells; remainder derma	24.0^{2}	1.5^{4}	1.4^{2}	0.89^{2}	1.0^{2}	4.5	−0.5	0.3
		20.9^{2}	2.3^{4}	1.8^{2}	0.86^{2}	3.3^{1}	2.1	−4.3	0.4
Hyperplastic skin (belly, induced with acetone-turpentine) (11)	About 15-25% normal and proliferating epidermal cells; remainder derma								

Measurements made at 38° C., pH 7.4, in Warburg-Okamoto Ringer solution (0.025 *M* $NaHCO_3$); 0.2% glucose in Warburg or Summerson manometers.
Q values represent cmm./hr./mgm. initial (aliquot) dry weight of tissue; superscripts refer to number of manometric determinations made, subscripts to number of tumors examined.
* S. E. for mean values of 10.2 and 6.9 = ± 0.34 and ±0.32 respectively; P value for difference of means is less than 0.01.
† Numbers in parentheses indicate references.

Oxygen consumption response of malignant, benign, and normal rabbit tissues to succinate and paraphenylenediamine.—It will be seen from Table II that the 3 transplanted cancers (V2 carcinoma, Brown-Pearce carcinoma, and rabbit sarcoma I) yielded average Q_{O_2} values in the presence of glucose that of normal adult cottontail rabbit tissues, and a series of 12 to 17 day old chick embryo tissues of the types reported in Table II for the domestic rabbit, likewise gave Q_{O_2} values that were in general increased one to several fold by paraphenylenediamine. The greatest percentage responses usually, but not always, came from

TABLE II: OXYGEN CONSUMPTION (Q_{O_2}) * RESPONSE OF MALIGNANT, BENIGN, AND NORMAL RABBIT TISSUES TO PARAPHENYLENEDIAMINE AND SUCCINATE IN GLUCOSE-PHOSPHATE MEDIUM

	Paraphenylenediamine (1 mgm./cc.)					Succinate (0.02 M)				
Domestic rabbit tissue	No. of determinations †	Minus	Plus	Increase	Percentage increase	No. of determinations †	Minus	Plus	Increase	Percentage increase
Neoplastic										
V2 carcinoma	11 (4)	2.9	5.0	2.2	69	5 (4)	2.1	2.8	0.7	36
Brown-Pearce carcinoma	4 (2)	4.2	7.5	3.3	85	3 (2)	4.2	5.6	1.4	34
Andrewes-Ahlström sarcoma (RS)I	3 (2)	3.8	8.4	4.6	119	4 (2)	4.2	5.4	1.2	28
Benign Shope virus papilloma (3-32 wks.)										
Domestic rabbit	16 (11)	2.4	3.3	1.4	63	9 (7)	2.2	2.6	0.4	22
(Wild cottontail rabbit)	7 (5)	2.3	3.5	1.2	52	3 (3)	2.9	2.6	0.2	4
Virus-induced fibroma (Shope) §	7 (3)	1.2	1.9	0.8	64	3 (1)	1.6	2.1	0.5	29
Keratinized papilloma (90-100% maturated squames; remainder living pap. cells)	6 (3)	0.4	1.0	0.6	154					
V2 "stroma" (70-85% nonneoplastic stroma; remainder V2 carcinoma cells)	9 (4)	2.5	7.1	4.6	191					
Normal										
Spleen	2	1.6	3.4	2.0	122	1	1.7	3.3	1.6	94
Lung	1	2.2	6.5	4.3	195	1	3.0	5.0	2.0	67
Skin	3	0.5	1.2	0.7	198	5	0.5	1.1	0.6	136
Embryonic liver (17 days)	2	2.2	7.4	5.2	248	1	2.1	4.2	2.1	100
Pancreas	1	0.5	1.8	1.3	265					
Kidney cortex	2	3.5	13.2	9.4	300	1	3.7	14.3	10.6	287
Kidney medulla	2	3.7	14.9	11.2	305	1	3.9	17.5	13.6	348
Brain	1	1.2	5.2	4.0	330	1	1.1	5.4	4.3	390
Retina	1	2.4	10.7	8.3	345	1	3.4	5.4	2.0	59
Ovary	2	1.9	8.3	6.5	345	1	2.3	11.3	9.0	390
Adult liver	4	1.3	6.4	5.1	430	5	1.2	9.5	8.6	900
Voluntary muscle (leg)	2	0.2	1.8	1.7	845	1	0.2	4.1	3.9	2,100
Adrenal gland	2	1.0	9.0	8.0	835	1	1.0	8.3	7.3	730
Heart muscle	2	0.9	12.4	11.6	1,510	1	1.0	3.1	2.1	210
Diaphragm fascia	1	0.1	0.9	0.8	1,720	1	0.1	1.2	1.1	2,340
Diaphragm muscle	2	0.1	11.4	11.3	7,360	1	0.1	15.8	15.7	8,900

* Q_{O_2} = cmm. O_2 consumed/mgm. initial aliquot dry weight/hr. "Minus" and "plus" Q_{O_2} values are averages of individual determinations based on readings taken for respectively 1 hour before and ½ to 1 hour after adding succinate or paraphenylenediamine from vessel side arm to a given tissue slice sample. Thus a given sample served to give a plus as well as minus value. The average increases and percentage increases in Q_{O_2} due to succinate and paraphenylenediamine have been calculated from averages of such individual determinations, not from the difference in the average minus and plus values reported.

† Values in parentheses refer to number of tumors studied.

§ The fibroma, though composed of proliferating fibroblasts, regresses after a time and is scarcely to be considered neoplastic.

were increased 120 per cent at the most upon the addition of paraphenylenediamine, and less than 40 per cent by succinate. The respective increases with the benign Shope virus papilloma and the virus-induced fibroma were also low. Similar tests with a number of normal domestic rabbit tissues, including embryonic liver, showed, however, that the Q_{O_2} of these was stimulated much more by paraphenylenediamine and succinate than were the neoplastic tissues. In subsidiary experiments not reported in detail here, a series the tissues having the lowest Q_{O_2} values in the absence of the added stimulators (Table II).

Salter and his colleagues have already called attention to the fact that the Q_{O_2} of tumor tissues in glucose-phosphate medium in general increases less in response to paraphenylenediamine or succinate than does the Q_{O_2} of normal tissues of homologous types (9, 18, 22). In a study of the Shope virus papilloma, Craig, Bassett, and Salter (9) recorded observations on four specimens of papilloma tissue procured at successive biop-

sies between the sixth and 14th weeks following virus inoculation. Their first 2 specimens (at 6 and 7 weeks) were described as "pre-papillomatous" lesions, and they yielded Q_{O_2} values in glucose phosphate of 1.07 and 0.28, respectively, which were increased two to fourfold upon addition of succinate or paraphenylenediamine. The subsequent specimens, procured 10 and 14 weeks after virus inoculation, were histologically benign papillomas of characteristic sort, and they gave Q_{O_2} values of 3.0 and 3.2 (average of two determinations) respectively, which were not increased upon addition of either of the substrates. In a subsequent paper (18), they report further observations on tissues procured after 46, 55, and 79 weeks; the first two of these specimens were benign papillomas while the last (79th week) was carcinomatous. All three materials yielded Q_{O_2} values (averaging around 4.3) that were not notably increased by paraphenylenediamine and succinate. From these observations, Salter and his colleagues have concluded that in the benign papilloma ". . . . a loss of cytochrome system response occurred rather abruptly after several weeks, and before histological evidence of frank malignancy was present" (9).

While our findings agree in general with those of Salter and his colleagues, in that the normal tissues studied (including embryonic ones) usually gave a greater oxygen consumption response to added paraphenylenediamine and to succinate than did neoplastic tissues of homologous sorts, still they differ notably in one important particular: There was no significant difference in the Q_{O_2} response of young and old papillomas to the added substrates. Determinations were made on papillomas from 9 rabbits 3 to 4 weeks after virus inoculation when the growths were raised 1 to 3 mm. above the surrounding skin—the earliest stage at which any considerable mass of papilloma tissue is available for slicing—and on the papillomas from 5 rabbits 11 to 32 weeks after virus inoculation (when the growths were raised 6 to 12 mm.). The average Q_{O_2} value for the younger papillomas was 2.2 (range, 1.4 to 3.1), and this was increased 56 per cent (range, 10 to 135) by paraphenylenediamine, and 14 per cent (range, −21 to 51) by succinate. The older growths also gave an average Q_{O_2} value of 2.2 (range, 1.9 to 3.4), which was increased 81 per cent (range, 18 to 112) by paraphenylenediamine and 51 per cent (range, 36 to 65) by succinate. It seems plain that the benign virus papillomas produced in domestic rabbits give, from a very early state, low Q_{O_2} responses to added paraphenylenediamine or succinate, and that they do not differ in this respect from the homologous malignant V2 carcinoma derived from the papilloma. As bearing further on the low Q_{O_2} responses of tissues to the added substrates as a measure of their benign or malignant character, the fact deserves mention that the virus papillomas in wild cottontail rabbits, which only rarely become malignant (13), gave no greater Q_{O_2} responses to the added substrates (Table II) than did the domestic rabbit papillomas, which usually become cancerous, though after many months' growth (20, 21).

It should be pointed out also that our keratinized papilloma slices, which contained 90 to 100 per cent of maturated squames and 10 per cent or less of living papilloma cells, yielded Q_{O_2} values averaging 0.4 that were increased 154 per cent by paraphenylenediamine, proving similar in these respects to the 6 and 7 weeks' "pre-papillomatous lesions" of Salter and his group (9, 18), and conforming in general to the pattern of the normal tissues. Much the same proved true of the V2 carcinoma slices that contained a preponderance of stroma, these yielding Q_{O_2} values averaging 2.5 that were stimulated 191 per cent (average) by the paraphenylenediamine. The virus-induced fibroma, on the other hand, which is not strictly neoplastic (23), provided slices that gave Q_{O_2} values averaging 1.2, which were increased less than 100 per cent by paraphenylenediamine and were like the generality of tumor tissues in this respect.

Warren has recently observed (25) that normal rabbit bone marrow and normal rabbit and rat kidney gave Q_{O_2} responses that were increased less than 100 per cent by added paraphenylenediamine and succinate. The kidney Q_{O_2} values in the absence of stimulator were so great (6 to 12 as privately communicated by Dr. Warren), however, that no larger percentage response could be expected, since, as Warburg's diffusion formula indicates, tissue slices can scarcely exceed Q_{O_2} values of 10 to 15 under customary technical conditions (1 atmosphere O_2, slices a few tenths of a millimeter thick, etc.). The high percentage stimulation of the rabbit kidney reported in Table II was obtained with specimens whose Q_{O_2} was well below 6, whereas a specimen of wild rabbit kidney with a Q_{O_2} of 11 was observed to give a stimulation of only 29 per cent. The various findings just discussed would seem to illustrate some of the limitations of the Q_{O_2} response of tissues to added paraphenylenediamine and succinate as a criterion in the diagnosis and study of neoplasms as distinct from normal and pathologically altered, nonneoplastic tissues.

Incidental observations.—Polarographic determinations of blood proteose (27) gave average values as follows, in arbitrary galvanometer deflection units. Twenty-one normal rabbits, 1.0 (range, 0.5 to 2); 3 rabbits with Shope papilloma virus of 3 weeks' duration, 1.0 (range, 1.0 to 1.0); 10 rabbits bearing

Shope papillomas of 10 to 32 weeks' duration, 2.0 (range, 1.0 to 3.0); 19 rabbits bearing V2 carcinomas of 10 days' to 10 weeks' duration, 4.4 (range, 3 to 8, the animals having older and larger growths in general giving the higher values); and 5 rabbits bearing Brown-Pearce carcinomas of 3 weeks' duration, 2.6 (range, 2 to 4). These findings are being considered elsewhere (27), along with a discussion of blood proteose values in relation to the problem of malignancy.

A large number of biotin and miotin (7) analyses were made by yeast bioassay of representative samples of the rabbit skin, hyperplastic skin, Shope virus papilloma, and V2 carcinoma materials used for metabolism studies. The skin materials contained an average of 0.08 microgram of biotin per gram dry weight (7 determinations), the values being similar to those reported by West and Woglom (26), who used Rhizobium rather than yeast as the bioassay organism. The papillomas and carcinomas gave the same average values for total biotin of about 0.13 microgram per gram dry weight (15 determinations each), West and Woglom having reported values of about 0.36 microgram for both materials. The miotin content of the V2 carcinomas ranged from 10 to 33 per cent of the total biotin, whereas that of the papillomas ranged from 6 to 15 per cent, and that of the skin from 2 to 9 per cent. A great variety of normal tissues from different species have yielded miotin values (7) of about 1 to 5 per cent of the total (range, 0.1 to 10 per cent). The comparatively high miotin content of the V2 carcinoma suggests that an altered biotin metabolism may be involved in the cells of this growth, but this remains problematical.

SUMMARY AND COMMENT

Data have been procured that indicate that the cells of the V2 rabbit carcinoma possess a glycolyzing capacity which, calculated on a dry weight basis, is about as great as that of the cells of 2 other transplanted rabbit cancers (the Brown-Pearce carcinoma and sarcoma I of Andrewes and Ahlström), and considerably greater than that of the benign virus papilloma cells of the sort from which they originally derived. The derived metabolic quotients, which relate glycolysis to oxygen consumption independently of dry weight, lend further support to the view that the metabolism of the V2 carcinoma cells is characteristic of malignant cells generally (4-6), whereas that of the Shope virus papilloma is characteristic of benign tumor cells and distinguishable in certain respects from that of normal rabbit skin cells. The differences in metabolism between the benign papilloma cells and the homologous V2 carcinoma cells are the more noteworthy since the former proliferate quite as rapidly as the latter. It remains to be ascertained whether the metabolic differences have something to do with the differences in the form and behavior of the papilloma and carcinoma cells, with the failure of repeated attempts to procure a causative virus from the V2 carcinoma (15), or with antigenic differences in the sedimentable constituents of the two sorts of cells (14-16).

Observations were also made on the oxygen consumption (Q_{O_2}) of certain normal and neoplastic rabbit tissues in glucose-phosphate medium with and without added paraphenylenediamine and succinate. The findings in general confirm the observations of others that normal tissues as a class give greater Q_{O_2} responses to the added substrates than do neoplastic tissues. The benign Shope virus papilloma, however, gave much the same low Q_{O_2} responses to the added substrates as did the homologous malignant V2 carcinoma, and this proved true also of the virus-induced fibroma, which is not actually neoplastic. Certain implications of the findings are discussed.

Polarographic determinations showed that rabbits carrying V2 carcinomas had greater amounts of protease in their blood than had rabbits with Shope papillomas of 3 weeks' duration or normal controls. There was no noteworthy difference in the biotin content of the benign papilloma and the malignant V2 carcinoma, as determined by yeast bioassay, though both types of tissues contained more biotin than did normal rabbit skin. The proportion of avidin-uncombinable biotin (miotin) was exceptionally high in the V2 carcinoma. The implications of these incidental observations will be considered elsewhere.

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Multiple Primary Malignant Tumors and Susceptibility to Cancer

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Experimental genetics has given us much information as to the part heredity and individual susceptibility play in the development of tumors in different strains of animals. Data from human material are less readily obtained and most of our knowledge has been based on reasoning by analogy from findings in animals, or on studies on the incidence of tumors, especially with regard to the occurrence of multiple malignant tumors, in given samples of a population. As time passes the accumulation of this type of data, in itself of individual and perhaps minor importance, may become significant from the point of view of human genetics.

The first thorough study of multiple primary malignant tumors was that of Warren and Gates (19), who concluded that the incidence was greater than could be explained on the basis of chance. Their statistical work was based on a group of 1,078 cancer autopsies, during which 40 (3.7 per cent) examples of primary malignant growths were found. In addition these authors analyzed cases collected from the literature, which together with their own totaled 1,259. The incidence of multiple malignant growths on the basis of European and American data was 1.8 per cent; on the basis of American data, it was 3.9 per cent.

A review of some of the more notable reports on the subject during the past ten years shows the interest it has aroused and may suggest new approaches.

In 1934 Bugher (2) presented 30 cases of multiple malignant neoplasms among 983 cases of cancer [1] autopsied at the University of Michigan Hospital from 1896 to 1932, an incidence of 3.1 per cent. Also, he analyzed the data of Warren and Gates (19), using different statistical methods, and obtained results in agreement with theirs. He concluded that the actual incidence of multiple cancers exceeds that expected on the basis of chance alone, and that there is an inherent susceptibility to cancer possessed by a portion of the population.

A somewhat smaller series than Bugher's, but perhaps more significant because of better histories as a result of the increased interest in cancer in recent years, was presented by Burke (3) from the University of Wisconsin Hospital, covering the period from 1924 to 1935. In 583 cancer autopsies, he found 46 (7.8 per cent) multiple cancers. In a series of 685 cancer autopsies at the Presbyterian Hospital, New York City, Hellendall (8) found 30 cases (4.3 per cent) of multiple malignant tumors.

Three other series recently reported gave rather lower figures than these. Austin (1), at Cincinnati, found an incidence of 2.7 per cent among 887 cancer autopsies; Kirshbaum and Shively (10), at Cook County Hospital, found 1.2 per cent among 1,411; and Tullis (18), at Bellevue Hospital, found 2 per cent among 1,044 autopsies on persons with cancer. The two latter low figures may be explained, perhaps, by less detailed case histories, so that cases of metachronous cancers were not readily recognized.

An even richer source of information might be found in surgical material, were it not for the difficulty in obtaining accurate historical data. The importance of a sufficiently long follow-up in a series of multiple malignant neoplasms based on surgical material is brought out by Regaud's (15) findings with two groups of cases of carcinoma of the cervix. In one group of 1,009 cases that were followed for a short period he found only 9 multiple malignant growths (0.9 per cent), whereas in 284 that had been followed for 5 to 6 years there were 6 cases (2.1 per cent). Hurt and Broders (9) reported 71 cases of multiple malignant growths among 2,124 cases of cancer treated at the Mayo Clinic in 1929. These authors felt that the incidence, 3.3 per cent, may be low, since their cases were followed only 2 years after treatment of the primary tumor. Later, Stalker, Phillips, and Pember-

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[1] Throughout the paper "cancer" is used in the general sense of a malignant tumor. Carcinoma is used for a malignant tumor of epithelial cells. Sarcoma for tumors of mesothelial origin.

ton (17) presented 2,500 cases with proved cancer, operated upon at the Mayo Clinic in 1937. Of these, 113, or 4.5 per cent, were cases of multiple malignant neoplasms (51 synchronous and 62 metachronous). They included 17 cases of bilateral lesions of breasts or ovaries.

From 1913 to 1933, among 11,212 cases of malignant neoplastic disease studied at the New York State Cancer Institute, 307 cases (2.7 per cent) of multiple cancers were encountered (16).

Gaudin (6) carried out a careful survey of 4,610 cancer patients in New Zealand covering a 40 year period; all but 71 were traced. Among them were 256 cases (5.5 per cent) of multiple malignant tumors. In the Liége, Belgium, Cancer Clinic, 3,115 cases of cancer were studied between 1925 and 1935. Only those multiple cases involving different systems were reported, thus reducing the number to 36, or 1.2 per cent (5). Hartmann (7) presented his personal experience of about 3,000 cancer patients, of whom 25 were histologically proved to have multiple cancers.

Most of these authors found a relatively high incidence of multiple malignant growths, and all attributed them to a susceptibility or predisposition to cancer.

Peller (13), however, presented statistical material to maintain a contention that he had previously presented, to wit: that a cured cancer secured protection against the appearance of another cancer. In support of this hypothesis he presented 5,876 cancer cases collected from several institutions. Among these there were 270 cases (4.6 per cent) of multiple malignant tumors. However, he based his statistical studies on the cases of metachronous multiple malignant neoplasms, that is, on only 40 out of the 270 cases. In each case, one of the cancers was on the skin. He concluded that the real rate for multiple malignant growths was less than the expected rate. It is obvious that the determination of whether two or more tumors have occurred simultaneously or metachronously is difficult and subject to error, even with careful histories and autopsy material. Warren and Gates (20), and more recently Lombard and Warren (11), have analyzed these and other statistics and pointed out a probable fallacy in Peller's conception of cancer protection. Furthermore, Warren and Gates (20), in their study of 1,149 cases of skin cancer, found that the cancer attack rate of organs other than the skin was twice that of the expected rate.

The importance of cutaneous carcinoma in multiplicity has been shown by many writers. Phillips (14), working in the American Southwest, studied a group of about 1,400 cases of skin cancer, of which 226, or 16 per cent, were multiple, ranging from 2 to 23 per patient. The majority, though not all, of the multiple lesions were primary. In discussing Phillips' paper, Cooper (4) stated that 1,790 cases of cutaneous cancer were seen at the Barnard Free Skin and Cancer Hospital between June 1936 and June 1941. The multiplicity rate was 5.9 per cent. In Gaudin's (6) series of multiple malignant tumors from New Zealand, there were 229 out of 256 cases of primary lesions in the skin. About one-fifth of the total number of patients with cancer of the skin had more than one primary malignant neoplasm. The strikingly high proportion of multiple cutaneous cancer in the studies of Gaudin and Phillips is no doubt due to its prevalence in the regions in which the surveys were made.

The concept of the susceptibility of a particular organ or tissue to cancer was well developed by Lund (12). In a series of 1,548 cases of cancer of the mouth studied at C. P. Huntington Memorial Hospital, he found 94 multiple cases (6 per cent); of these 31 had multiple cancer of the buccal mucosa, about 15 times the number expected on the basis of chance alone.

Present Series

Among the several considerations that will affect the computed incidence of multiple primary malignant growths, the advances in methods of tumor diagnosis and in end-result studies are fundamental. The trend of the investigations published in recent years suggests that thorough studies of multiple primary malignant neoplasms in the future may be expected to give an even greater preponderance of observed over expected multiple cases.

We are presenting our experience from 2,829 consecutive autopsies on cases of cancer performed in the laboratories of the C. P. Huntington Memorial Hospital, New England Deaconess Hospital, Pondville State Hospital, and Westfield State Sanatorium (Cancer Division) from January 1932 through December 1943. There are 194 cases of multiple malignant tumors. These are recorded on Tables I to X and summarized in Table XI.

This series is a continuation of the earlier one of 1,078 cases reported in 1932 by Warren and Gates (19), which covered a period from 1926 through 1931. The incidence of multiple primary malignant growths in the present series is almost double that of the first: 6.8 per cent as against 3.7 per cent. This probably is a reflection of the current awareness to cancer, which results in more complete clinical histories and an increased tendency to submit radiologically treated tumors to biopsy and to require histologic examination of all tumors excised. The incidence of both series together, comprising 3,907 cases, is 6 per cent. The material in each series has been handled in a similar manner, with only minor exceptions. The data in all the cases were adequate, and in the majority of

Table I: Cases of Four Malignant Tumors

Number	Sex	First cancer							Second cancer							Third cancer							Fourth cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A. Skin:																															
A-39-62	♂	50	Skin, forehead	Basal-cell carcinoma	−	−	−	20.0	0.0	50	Skin, right cheek	Basal-cell carcinoma	−	−	−	20.0	0.0	50	Skin, right	Basal-cell carcinoma	−	−	−	20.0	19.6	70	Skin, sternum	Basal-cell carcinoma	−	−	−	0.4
B. Miscellaneous:																															
29,700	♀	49	Ovary, left	Papillary adenocarcinoma	−	+	−	3.0	0.0	49	Uterus	Adenocarcinoma	−	−	−	3.0	0.0	49	Cecum	Adenocarcinoma	−	−	−	3.0	0.0	49	Cecum	Malignant polyp	−	−	−	3.0
37-A-195	♂	61	Lip, lower	Epidermoid carcinoma, grade I	−	−	−	6.0	4.8	66	Skin, right face	Epidermoid carcinoma, grade I	−	−	··	1.3	0.8	67	Skin, right	Epidermoid carcinoma, grade I	+	−	−	0.5	0.0	67	Skin, right	Epidermoid carcinoma, grade I	−	−	−	0.5
34-A-40	♂	66	Lip, lower	Epidermoid carcinoma, grade I	+	+	−	5.0	4.5	71	Bladder	Epidermoid carcinoma, grade II	+	−	−	0.5	N.S.	71	Stomach	Adenocarcinoma	+	−	−	N.S.	N.S.	71	Prostate	Adenocarcinoma	+	−	−	N.S.
A-40-62	♂	67	Rectum	Malignant adenoma	−	−	−	0.7	0.0	67	Colon, transverse	Adenocarcinoma	+	−	−	0.7	0.0	67	Colon, ascending	Malignant adenoma	+	−	−	0.7	N.S.	67	Pancreas	Early carcinoma	+	−	−	N.S.
43-A-49	♂	73	Mouth, right palate	Epidermoid carcinoma, grade III	−	+	−	1.0	N.S.	74	Stomach	Adenocarcinoma	+	+	−	N.S.	N.S.	74	Esophagus, upper 1/3	Epidermoid carcinoma, grade III	+	+	−	N.S.	N.S.	74	Esophagus, lower 1/3	Epidermoid carcinoma, grade III	+	+	−	N.S.

In Tables I to X:

N.S. = not stated.
+ = histologically verified metastases excised.
− = lymph nodes removed and proved negative on microscopic examination; or, assumed metastases treated by radiation.
* = metastases found at autopsy could be attributed to one of or all the malignant tumors.

Table II: Cases of Three Malignant Tumors

TABLE II: CASES OF THREE MALIGNANT TUMORS

Number	Sex	First cancer							Second cancer								Third cancer							
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A. Skin:																								
37-A-132	♀	67	Skin, face	Basal-cell carcinoma	+	−	−	15.0	12.0	79	Skin, left arm	Mixed basal and epidermoid carcinoma	+	−	−	3.0	1.6	81	Skin, right leg	Basal-cell carcinoma	+	−	−	1.4
B. Gastrointestinal tract (large intestine):																								
A-41-4	♂	59	Sigmoid	Adenocarcinoma	+	+	−	1.5	0.0	59	Colon, transverse	Adenocarcinoma	+	−	−	1.5	N.S.	60	Rectum	Malignant adenoma	+	−	−	N.S.
39,023	♀	61	Cecum	Adenocarcinoma	−	*	−	2.6	N.S.	63	Sigmoid	Adenocarcinoma	+	*	−	N.S.	N.S.	63	Rectum	Adenocarcinoma	+	*	−	N.S.
52,627	♀	76	Rectum	Adenocarcinoma	−	−	−	1.7	1.5	77	Colon, ascending	Adenocarcinoma	+	+	−	0.2	N.S.	77	Colon, ascending	Malignant adenoma	+	−	−	N.S.
C. Miscellaneous:																								
34-A-76	♀	33	Ovaries	Malignant papillary adenocystoma	−	−	+	8.0	7.0	40	Cervix	Epidermoid carcinoma, grade II	−	+	−	1.0	N.S.	41	Ileum	Adenocarcinoma	+	−	−	N.S.
59,381	♀	48	Breast, left	Carcinoma simplex	−	+	+	2.6	1.0	49	Breast, right	Carcinoma simplex	+	−	−	1.6	N.S.	50	Bronchus	Epidermoid carcinoma, grade II	+	−	−	N.S.
35-1988	♂	53	Uvula and hard palate	Epidermoid carcinoma, grade II	−	−	−	11.0	8.0	61	Tongue	Epidermoid carcinoma, grade III	−	−	−	3.0	2.8	64	Pyriform sinus	Epidermoid carcinoma, grade III	−	−	−	0.2
60,431	♀	53	Uterus	Leiomyosarcoma	−	+	−	5.0	0.0	53	Ovary	Mucinous papillary adenocarcinoma	−	+	−	5.0	3.0	56	Lymphoid tissue	Lymphatic leukemia	+	+	−	2.0
34-A-17	♂	60	Skin, upper face	Basal-cell carcinoma	−	−	−	8.0	7.7	68	Lymphoid tissue	Lymphoma	+	+	−	0.3	N.S.	68	Prostate	Adenocarcinoma	+	−	−	N.S.
A-39-11	♂	64	Lip, lower	Epidermoid carcinoma, grade II	−	−	−	3.0	N.S.	67	Prostate	Adenocarcinoma	+	−	−	N.S.	N.S.	67	Sigmoid	Malignant adenoma	+	−	−	N.S.
37-A-75	♂	65	Prostate	Carcinoma simplex	+	+	−	8.0	6.0	71	Sigmoid	Adenocarcinoma	+	+	−	2.0	0.0	71	Rectum	Malignant adenoma	+	−	−	2.0
47,948	♂	66	Tonsil, left	Epidermoid carcinoma, grade II	+	+	+	1.5	N.S.	67	Kidney, left	Renal cell carcinoma	+	−	−	N.S.	N.S.	67	Prostate	Adenocarcinoma	+	−	−	N.S.
37-A-41	♂	66	Lip, lower	Epidermoid carcinoma, grade II	−	−	−	9.5	8.7	74	Bladder	Epidermoid carcinoma, grade II	+	−	−	0.8	0.0	74	Alveolus	Epidermoid carcinoma, grade II	+	−	−	0.8
38-A-9	♀	67	Ovary, right	Papillary adenocarcinoma	−	+	+	0.5	N.S.	67	Cecum	Adenocarcinoma	+	−	−	N.S.	N.S.	67	Lymph node	Hodgkin's disease	+	+	−	N.S.
19,862	♀	67	Breast, left	Carcinoma simplex	−	+	+	3.0	N.S.	67	Pancreas	Adenocarcinoma	+	+	−	N.S.	N.S.	70	Uterus	Leiomyosarcoma	+	−	−	N.S.
40-A-23	♂	69	Skin, left neck	Basal-cell carcinoma	−	−	−	1.0	0.1	69	Tonsil and tongue	Epidermoid carcinoma, grade II	+	+	−	0.9	0.4	70	Lip, lower	Epidermoid carcinoma, grade II	−	−	−	0.4
41,976	♂	72	Lip, lower	Epidermoid carcinoma, grade II	−	+	+	2.0	0.0	72	Skin, right ear	Epidermoid carcinoma, grade N. S.	−	+	+	2.0	N.S.	74	Spleen	Malignant lymphoma	+	−	−	N.S.
41-A-49	♂	73	Prostate	Carcinoma simplex	+	+	−	2.0	N.S.	75	Colon, ascending	Adenocarcinoma	+	−	−	N.S.	N.S.	75	Colon, ascending	Adenocarcinoma	+	−	−	N.S.
35-A-55	♂	73	Breast, left	Carcinoma simplex	−	+	+	2.0	N.S.	75	Rectum	Adenocarcinoma	+	−	−	N.S.	N.S.	75	Prostate	Adenocarcinoma	+	−	−	N.S.
37-A-171	♂	74	Skin, temporal region	Mixed basal and epidermoid carcinoma	−	−	−	4.0	0.5	75	Hard palate	Epidermoid carcinoma, grade N. S.	−	−	−	3.5	3.3	78	Esophagus	Epidermoid carcinoma, grade II	+	+	−	0.2
43-A-18	♂	74	Mouth, floor	Epidermoid carcinoma, grade III	−	−	−	5.8	4.0	78	Colon, splenic flexure	Adenocarcinoma	+	+	−	1.8	N.S.	80	Prostate	Adenocarcinoma	+	−	−	N.S.
A-39-37	♀	77	Uterus	Adenocarcinoma	−	−	−	2.5	0.0	77	Uterus	Leiomyosarcoma	−	−	−	2.5	2.0	79	Breast, left	Carcinoma simplex	−	−	+	0.5
36-A-14	♂	85	Skin, hand	Basal-cell carcinoma	−	−	−	2.0	1.8	87	Lip, lower	Epidermoid carcinoma, grade I	+	−	−	0.2	N.S.	87	Kidney, pelvis	Transitional cell carcinoma	+	−	−	N.S.

TABLE III: DOUBLE CARCINOMAS OF THE SAME ORGAN

Number	Sex	First cancer							Interval	Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A. Skin:																
A-38-56	♂	76	Skin, body	Epidermoid carcinoma, grade II	−	+	+	0.3	N.S.	76	Skin, N. S.	Early carcinoma	+	−	−	N.S.
37-A-71	♂	79	Skin, right face	Basal-cell carcinoma	+	−	−	4.0	0.0	79	Skin, nose	Basal-cell carcinoma	+	−	−	4.0
43-A-51	♂	81	Skin, right postauricular	Basal-cell carcinoma	−	−	−	5.0	0.0	81	Skin, left lower face	Epidermoid carcinoma, grade I	−	−	−	5.0
B. Pharynx:																
40-A-1	♂	74	Lip, lower	Epidermoid carcinoma, grade I	−	−	−	3.0	0.0	74	Mouth	Epidermoid carcinoma, ungraded	−	−	−	3.0
C. Large intestine:																
38-A-7	♂	42	Cecum	Adenocarcinoma	−	−	−	N.S.	N.S.	42	Rectum	Adenocarcinoma	−	+	+	N.S.
A-40-34	♂	50	Rectum	Malignant adenoma	−	−	−	0.6	0.0	50	Sigmoid	Adenocarcinoma	−	+	+	0.6
25,326	♀	52	Colon, ascending	Adenocarcinoma	−	+	+	1.5	N.S.	53	Rectum	Malignant adenoma	+	−	−	N.S.
42-A-48	♂	57	Colon, transverse	Adenocarcinoma	+	*	−	2.0	0.0	57	Colon, transverse	Adenocarcinoma	+	*	−	2.0
38-A-4	♂	59	Rectum	Mucinous adenocarcinoma	−	+	+	1.0	0.0	59	Rectum	Malignant adenoma	−	−	−	1.0
49,924	♂	60	Rectum	Adenocarcinoma	−	−	−	1.0	0.0	60	Colon, splenic flexure	Adenocarcinoma	−	−	−	1.0
39-A-80	♀	61	Colon, splenic flexure	Adenocarcinoma	−	−	−	4.0	N.S.	65	Rectum	Adenocarcinoma	−	−	−	N.S.
39-A-145	♀	62	Colon	Adenocarcinoma	+	−	−	0.8	N.S.	62	Rectum	Malignant polyp	+	−	−	N.S.
39-A-68	♂	64	Colon, descending	Adenocarcinoma	+	*	−	0.5	0.0	64	Colon, hepatic flexure	Adenocarcinoma	+	*	−	0.5
62,183	♂	64	Sigmoid	Adenocarcinoma	+	*	−	0.3	0.0	64	Rectum	Adenocarcinoma	+	*	−	N.S.
32-A-80	♂	65	Sigmoid	Adenocarcinoma	−	−	N.S.	5.0	4.5	70	Colon	Adenocarcinoma	−	−	−	0.5
42,286	♂	68	Colon, transverse	Adenocarcinoma	−	+	+	0.5	0.0	68	Rectum	Malignant adenoma	+	−	−	0.5
A-38-27	♂	68	Rectum	Adenocarcinoma	+	+	−	0.6	0.0	68	Rectum	Malignant adenoma	+	−	−	0.6
29,627	♂	69	Sigmoid	Malignant adenoma	−	−	−	N.S.	N.S.	69	Colon, splenic flexure	Adenocarcinoma	+	−	−	N.S.
36-A-124	♀	75	Rectum	Adenocarcinoma	+	*	−	1.7	N.S.	76	Cecum	Adenocarcinoma	+	*	−	N.S.
37-A-162	♂	78	Rectum	Adenocarcinoma	−	−	−	0.3	0.0	78	Rectum	Malignant adenoma	−	−	−	0.3

TABLE IV: DOUBLE SARCOMAS

Number	Sex	First cancer							Interval	Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A. Of the same systems:																
41-3589	♂	35	Lymph node	Hodgkin's disease	+	+	−	2.0	2.0	37	Granulopoietic tissue	Myelogenous leukemia	+	+	−	N.S.
41-A-75	♀	60	Bone, humerus	Osteogenic sarcoma	+	+	−	N.S.	N.S.	60	Bone, pelvis	Osteogenic sarcoma	+	−	−	N.S.
B. Of different systems:																
55,706	♂	26	Nerve, trunk	Neurogenic sarcoma	+	+	−	10.0	N.S.	36	Granulopoietic tissue	Myelogenous leukemia	+	+	−	N.S.
36-A-126	♂	72	Lymphoid tissue	Lymphatic leukemia	+	+	−	0.6	0.0	72	Skin, cheek	Malignant melanoma	−	+	−	0.6

TABLE V: DOUBLE CARCINOMAS OF SYMMETRICAL ORGANS

Number	Sex	First cancer							Interval	Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A. Female breasts:																
43-A-33	♀	43	Breast, right	Carcinoma simplex	−	+	+	2	N.S.	45	Breast, left	Carcinoma simplex	+	+	−	N.S.
35-A-48	♀	45	Breast, right	Carcinoma simplex	−	+	+	5	4.0	49	Accessory breast, left axilla	Carcinoma simplex	−	−	−	1.0
32,640	♀	48	Breast, right	Carcinoma simplex	−	+	−	2	N.S.	50	Breast, left	Carcinoma simplex	+	+	−	N.S.
41,220	♀	55	Breast, left	Carcinoma simplex	−	+	+	2	1.5	57	Breast, right	Carcinoma simplex	−	+	+	0.5
43,766	♀	61	Breast, left	Carcinoma simplex	−	−	+	2	1.0	62	Breast, right	Carcinoma simplex	+	+	−	1.0

TABLE VI: DOUBLE CARCINOMAS OF THE SAME SYSTEM

Number	Sex	First cancer							Interval	Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A. Gastrointestinal tract:																
35-A-81	♂	55	Rectum	Adenocarcinoma	+	−	−	0.7	N.S.	55	Ampulla of Vater	Adenocarcinoma	+	−	−	N.S.
35-A-76	♂	56	Sigmoid	Adenocarcinoma	+	+	−	1.0	0.0	56	Stomach	Adenocarcinoma	+	−	−	1.0
49,039	♂	56	Colon, hepatic flexure	Adenocarcinoma	−	−	N.S.	13.0	11.0	67	Stomach	Adenocarcinoma	+	−	+	2.0
37,307	♂	59	Rectum	Carcinoma simplex	−	+	+	0.4	N.S.	59	Stomach	Adenocarcinoma	+	−	−	N.S.
35,631	♂	63	Rectum	Malignant adenoma	−	−	−	6.0	5.5	69	Esophagus	Epidermoid carcinoma, ungraded	+	−	−	0.5
A-41-10	♂	66	Esophagus	Epidermoid carcinoma, grade II	+	+	−	0.7	N.S.	67	Stomach	Adenocarcinoma	+	−	−	N.S.
34-A-122	♂	68	Sigmoid	Adenocarcinoma	+	+	−	1.0	N.S.	69	Stomach	Adenocarcinoma	+	−	−	N.S.
A-38-69	♂	71	Stomach	Malignant adenoma	+	−	−	1.3	1.0	72	Rectum	Adenocarcinoma	+	−	−	0.3
38-A-46	♀	76	Rectum	Adenocarcinoma	−	+	−	0.6	N.S.	76	Stomach	Adenocarcinoma	+	−	−	N.S.
B. Male genitourinary tract:																
34-A-172	♂	68	Bladder	Epidermoid carcinoma, grade III	+	+	−	2.5	N.S.	70	Prostate	Adenocarcinoma	+	−	−	N.S.
38-A-89	♂	68	Bladder	Carcinoma simplex	+	+	−	0.8	N.S.	68	Prostate	Adenocarcinoma	+	−	−	N.S.
48,792	♂	71	Bladder	Epidermoid carcinoma, grade III	−	+	−	1.0	0.0	71	Prostate	Carcinoma simplex	+	−	−	1.0
16,924	♂	72	Prostate	Carcinoma simplex	−	+	−	0.6	N.S.	72	Kidney	Adenocarcinoma	+	−	−	N.S.
37-A-144	♂	79	Prostate	Adenocarcinoma	+	−	−	1.3	N.S.	80	Kidney	Renal cell adenocarcinoma	+	−	−	N.S.
C. Miscellaneous:																
40-A-85	♂	70	Larynx	Epidermoid carcinoma, grade II	−	−	−	4.0	N.S.	74	Bronchus	Epidermoid carcinoma, grade III	+	+	−	N.S.

TABLE VII: DOUBLE CARCINOMAS OF DIFFERENT SYSTEMS

Number	Sex	First cancer							Interval	Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A. Skin and gastrointestinal tract:																
32-A-47	♂	55	Rectum	Adenocarcinoma	−	+	+	3.0	2.5	58	Skin, left ear	Epidermoid carcinoma, grade I	+	−	−	0.5
38-A-86	♂	58	Lip, lower	Epidermoid carcinoma, grade I	−	−	−	3.5	2.0	60	Rectum	Adenocarcinoma	−	+	−	1.5
33-A-129	♂	59	Skin, upper face	Basal-cell carcinoma	−	−	−	4.3	4.0	63	Esophagus	Epidermoid carcinoma, grade II	+	+	−	0.3
A-38-39	♂	61	Rectum	Malignant adenoma	+	−	−	0.3	N.S.	62	Skin, abdomen	Basal-cell carcinoma	+	−	−	N.S.
39-A-88	♂	66	Skin, cheek	Epidermoid carcinoma, grade I	−	−	−	2.7	2.5	69	Stomach	Adenocarcinoma	+	+	−	0.2
36-A-93	♂	71	Skin, right cheek	Basal-cell carcinoma	−	−	−	2.0	1.0	72	Stomach	Carcinoma simplex	+	+	−	1.0
26,585	♂	74	Cecum	Adenocarcinoma	−	−	−	0.2	N.S.	74	Skin, chest	Basal-cell carcinoma	+	−	−	N.S.
B. Skin and genitourinary tract:																
A-39-69	♀	55	Skin, nose	Basal-cell carcinoma	−	−	−	7.0	6.2	61	Bladder	Epidermoid carcinoma, grade III	+	−	−	0.8
69,531	♂	63	Skin, right nostril	Basal-cell carcinoma	−	−	−	2.0	N.S.	65	Prostrate	Carcinoma simplex	+	−	−	N.S.
34-A-15	♂	77	Skin, upper face	Epidermoid carcinoma, grade III	−	+	−	3.0	N.S.	80	Prostate	Adenocarcinoma	+	−	−	N.S.
38-A-33	♂	77	Prostate	Adenocarcinoma	+	−	−	0.3	0.0	77	Skin, forearm	Epidermoid carcinoma, grade I	−	−	−	0.3
34-A-82	♂	84	Skin, lower face	Basal-cell carcinoma	−	−	−	6.0	N.S.	90	Prostate	Adenocarcinoma	+	−	−	N.S.
C. Breast and skin:																
20,625	♀	57	Vulva	Epidermoid carcinoma, grade I	−	+	−	5.5	0.7	57	Breast, right	Colloid carcinoma	−	−	−	4.8
D. Breast and genitourinary tract:																
24,037	♀	50	Breast, right	Carcinoma simplex	−	−	+	12.0	10.0	60	Cervix	Epidermoid carcinoma, grade II	−	−	−	2.0
E. Breast and gastrointestinal tract:																
40-A-35	♀	48	Breast, left	Carcinoma simplex	−	−	−	2.8	2.0	50	Cecum	Adenocarcinoma	−	−	−	0.8
A-40-73	♀	51	Breast, right	Carcinoma simplex	−	+	+	4.3	N.S.	55	Duodenum	Papillary adenocarcinoma	+	+	−	N.S.
51,643	♀	73	Stomach	Carcinoma simplex	+	*	−	2.0	0.5	73	Breast, left	Adenocarcinoma	+	*	−	1.5
F. Genitourinary and gastrointestinal tracts:																
38-A-11	♂	26	Rectum	Mucinous adenocarcinoma	+	−	−	3.0	1.8	28	Bladder	Epidermoid carcinoma, grade III	+	−	−	1.2
36-A-72	♀	27	Cervix	Epidermoid carcinoma, grade II	−	+	−	1.0	N.S.	28	Cecum	Malignant adenoma	+	−	−	N.S.
37-A-38	♀	41	Rectum	Mucinous adenocarcinoma	−	+	+	2.3	0.8	42	Ovaries	Papillary adenocarcinoma	−	−	−	1.5
A-39-68	♀	42	Cervix	Epidermoid carcinoma, grade II	+	+	−	1.0	N.S.	43	Rectum	Malignant adenoma	+	−	−	N.S.
32-A-114	♀	51	Uterus	Adenoacanthoma	+	+	−	1.3	N.S.	52	Colon	Adenocarcinoma	+	−	−	N.S.
A-39-3	♀	52	Uterus	Adenocarcinoma	+	+	−	3.2	3.0	55	Stomach	Adenocarcinoma	+	−	−	0.2
59,645	♂	52	Colon, ascending	Adenocarcinoma	+	−	−	N.S.	N.S.	52	Prostate	Adenocarcinoma	+	−	−	N.S.
19,183	♀	54	Uterus	Adenocarcinoma	−	−	−	7.0	3.0	57	Cecum	Adenocarcinoma	+	−	−	4.0
58,521	♂	56	Esophagus	Adenocarcinoma	−	−	−	0.8	N.S.	57	Prostate	Adenocarcinoma	+	−	−	N.S.
68,340	♂	57	Esophagus	Epidermoid carcinoma, grade III	−	+	−	0.7	N.S.	58	Prostate	Adenocarcinoma	+	−	−	N.S.
32-A-107	♂	58	Stomach	Malignant adenoma	−	−	−	0.3	N.S.	58	Kidney	Renal cell adenocarcinoma	+	−	−	N.S.
35,924	♂	60	Stomach	Carcinoma simplex	−	−	+	0.3	N.S.	60	Prostate	Adenocarcinoma	+	−	−	N.S.
A-42-4	♂	60	Rectum	Carcinoma simplex	+	+	−	1.0	N.S.	61	Prostate	Adenocarcinoma	+	−	−	N.S.
42-A-26	♂	61	Rectum	Adenocarcinoma	−	−	+	1.0	0.3	62	Prostate	Adenocarcinoma	+	−	−	0.7

TABLE VII (*continued*)

Number	Sex	First cancer							Interval	Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
F. Genitourinary and gastrointestinal tracts—Continued:																
38-A-121	♂	61	Stomach	Carcinoma simplex	−	+	+	0.5	N.S.	61	Prostate	Adenocarcinoma	+	−	−	N.S.
33-A-84	♂	63	Rectum	Adenocarcinoma	+	+	−	1.0	N.S.	64	Bladder	Epidermoid carcinoma, grade II	+	−	−	N.S.
30,060	♀	63	Stomach	Adenocarcinoma	−	−	+	0.7	0.5	63	Cervix	Epidermoid carcinoma, grade II	−	−	−	0.2
37-A-88	♀	64	Cervix	Epidermoid carcinoma, grade II	−	−	−	1.0	0.7	65	Rectum	Adenocarcinoma	+	−	−	0.3
41-A-61	♂	65	Esophagus	Epidermoid carcinoma, grade III	+	+	−	1.0	N.S.	66	Prostate	Adenocarcinoma	+	−	−	N.S.
33-A-1	♀	65	Sigmoid	Adenocarcinoma	−	+	N.S.	2.5	2.0	67	Ovary	Adenocarcinoma	−	−	−	0.5
A-39-10	♂	67	Stomach	Carcinoma simplex	+	−	−	1.0	0.5	68	Bladder	Epidermoid carcinoma, grade I	+	+	−	0.5
62,725	♂	67	Rectum	Adenocarcinoma	+	−	−	4.0	N.S.	71	Prostate	Adenocarcinoma	+	−	−	N.S.
41,290	♂	67	Stomach	Carcinoma simplex	−	+	+	0.5	N.S.	67	Prostate	Adenocarcinoma	+	−	−	N.S.
51,781	♂	67	Cecum	Carcinoma simplex	+	*	−	0.3	N.S.	67	Prostate	Carcinoma simplex	+	*	−	N.S.
35-A-49	♂	68	Rectum	Carcinoma simplex	+	−	−	3.0	N.S.	71	Prostate	Carcinoma simplex	+	−	−	N.S.
37-A-151	♂	71	Esophagus	Epidermoid carcinoma, grade III	+	+	−	1.0	N.S.	72	Prostate	Adenocarcinoma	+	−	−	N.S
20,228	♂	73	Stomach	Carcinoma simplex	+	+	−	0.3	N.S.	73	Prostate	Adenocarcinoma	+	−	−	N.S.
37-A-200	♂	75	Sigmoid	Adenocarcinoma	−	+	+	0.2	N.S.	75	Prostate	Adenocarcinoma	+	−	−	N.S.
40-A-102	♂	75	Colon	Mucinous carcinoma simplex	+	−	−	0.5	N.S.	75	Prostate	Adenocarcinoma	+	−	−	N.S.
41-A-90	♂	75	Rectum	Adenocarcinoma	−	+	+	1.0	N.S.	76	Prostate	Adenocarcinoma	+	−	−	N.S.
46,753	♂	76	Sigmoid	Adenocarcinoma	+	−	−	0.6	N.S.	76	Prostate	Adenocarcinoma	+	−	−	N.S.
42-A-36	♂	77	Prostate	Adenocarcinoma	+	+	−	2.0	N.S.	79	Rectum	Malignant adenoma	+	−	−	N.S.
G. Miscellaneous:																
A-38-46	♂	30	Testis	Teratoma	+	+	+	0.3	N.S.	30	Adrenals	Carcinoma simplex	+	−	−	N.S.
29,972	♀	33	Uterus	Chorioepithelioma	−	+	−	0.6	N.S.	33	Thyroid	Papillary adenocarcinoma	+	+	−	N.S.
39-A-51	♀	44	Cervix	Epidermoid carcinoma, grade II	−	−	−	7.0	6.8	51	Liver, bile ducts	Carcinoma	+	+	−	0.2
40-A-52	♂	47	Pharynx	Epidermoid carcinoma, grade II	+	−	−	0.3	0.0	47	Esophagus	Epidermoid carcinoma, grade II	+	+	−	0.3
55,314	♂	48	Larynx	Epidermoid carcinoma, grade II	+	−	−	1.0	0.9	49	Rectum	Adenocarcinoma	−	−	+	0.1
25,156	♀	48	Thyroid	Carcinoma simplex	+	+	−	1.0	0.0	48	Esophagus	Epidermoid carcinoma, grade II	+	+	−	1.0
50,878	♂	52	Bronchus	Epidermoid carcinoma, grade III	+	−	−	1.0	N.S.	53	Prostate	Adenocarcinoma	+	−	−	N.S.
36-A-17	♂	52	Colon, descending	Adenocarcinoma	+	−	−	0.5	N.S.	52	Pancreas	Carcinoma simplex	+	−	−	N.S.
35-A-107	♂	52	Larynx	Epidermoid carcinoma, grade III	+	+	−	0.8	N.S.	53	Prostate	Adenocarcinoma	+	−	−	N.S.
18,574	♀	53	Cervix	Epidermoid carcinoma, grade III	−	−	−	8.0	7.5	61	Liver, bile ducts	Carcinoma	+	+	−	0.5
62,494	♂	54	Liver, bile ducts	Adenocarcinoma	+	+	−	1.0	N.S.	55	Prostate	Adenocarcinoma	+	−	−	N.S.
39-A-60	♀	54	Liver, bile ducts	Carcinoma	+	+	−	1.0	N.S.	55	Breast	Carcinoma simplex	+	−	−	N.S.
A-40-2	♂	56	Lung, left	Epidermoid carcinoma, grade II	+	+	−	0.5	N.S.	57	Skin, face	Basal-cell carcinoma	−	−	−	N.S.
34-A-92	♂	56	Pharynx	Epidermoid carcinoma, grade I	+	−	−	0.7	N.S.	56	Prostate	Early adenocarcinoma	+	−	−	N.S.

TABLE VII (*continued*)

Number	Sex	First cancer							Interval	Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
G. Miscellaneous—Continued:																
35-A-75	♂	56	Larynx	Epidermoid carcinoma, grade III	+	+	−	0.6	N.S.	56	Prostate	Adenocarcinoma	+	−	−	N.S.
41,704	♀	59	Breast, left	Carcinoma simplex	−	+	+	2.0	1.5	61	Thyroid	Papillary adenocarcinoma	−	−	+	0.5
43,839	♂	59	Tongue	Epidermoid carcinoma, ungraded	+	−	−	1.0	N.S.	60	Kidney, right	Adenocarcinoma	+	+	−	N.S.
45,082	♂	62	Pancreas	Adenocarcinoma	+	+	−	0.5	N.S.	62	Prostate	Adenocarcinoma	+	−	−	N.S.
35-A-10	♂	62	Lip, lower	Epidermoid carcinoma, grade I	−	+	−	2.0	N.S.	64	Stomach	Early adenocarcinoma	+	−	−	N.S.
32-A-27	♀	64	Skin, upper face	Mixed basal and epidermoid carcinoma	+	−	−	8.0	7.2	72	Mouth	Epidermoid carcinoma, grade I	+	−	−	0.8
39-A-53	♂	65	Rectum	Adenocarcinoma	+	+	−	0.3	N.S.	65	Lung, right	Bronchogenic carcinoma	+	−	−	N.S.
36-A-12	♀	66	Pharynx	Epidermoid carcinoma, grade II	+	−	−	1.5	N.S.	66	Stomach	Adenocarcinoma	+	−	−	N.S.
39-A-126	♂	66	Lip	Epidermoid carcinoma, grade I	−	−	−	14.0	13.8	80	Pancreas	Adenocarcinoma	+	+	−	0.2
32-A-19	♀	67	Mouth	Epidermoid carcinoma, grade I	+	+	−	0.8	N.S.	67	Esophagus	Epidermoid carcinoma, grade II	+	−	−	N.S.
34-A-121	♂	68	Bronchus	Epidermoid carcinoma, grade II	+	+	−	0.8	0.5	68	Colon	Adenocarcinoma	+	−	−	0.3
37-A-23	♂	69	Bronchus	Epidermoid carcinoma, ungraded	+	+	−	1.3	0.0	69	Stomach	Adenocarcinoma	+	−	−	1.3
42-A-59	♂	69	Alveolus, left upper	Epidermoid carcinoma, grade I	+	+	−	1.0	N.S.	70	Prostate	Adenocarcinoma	+	−	−	N.S.
A-39-43	♂	70	Larynx	Epidermoid carcinoma, grade II	+	−	−	0.6	0.5	70	Pancreas	Adenocarcinoma	+	+	−	0.1
35-A-66	♂	70	Mouth	Epidermoid carcinoma, grade III	+	+	−	1.5	N.S.	71	Prostate	Adenocarcinoma	+	−	−	N.S.
63,679	♂	72	Tongue and pharynx	Epidermoid carcinoma, grade II	+	+	−	N.S.	N.S.	72	Sigmoid	Adenocarcinoma	+	−	−	N.S.
43-A-47	♂	72	Tongue	Epidermoid carcinoma, grade I	−	−	−	3.0	N.S.	75	Prostate	Adenocarcinoma	+	−	−	N.S.
36-A-35	♂	74	Rectum	Malignant adenoma	+	−	−	2.6	1.6	75	Parotid, left	Carcinoma simplex	+	+	−	1.0
38-A-125	♂	75	Tongue	Epidermoid carcinoma, grade I	+	−	−	1.0	N.S.	76	Prostate	Adenocarcinoma	+	−	−	N.S.
A-41-2	♀	76	Breast, right	Carcinoma simplex	+	+	−	1.0	N.S.	77	Pancreas	Early carcinoma	+	−	−	N.S.
39-A-95	♂	77	Mouth	Epidermoid carcinoma, grade I	+	+	−	1.0	N.S.	78	Stomach	Malignant adenoma	+	−	−	N.S.
35-A-45	♂	77	Tongue	Epidermoid carcinoma, grade I	+	−	−	1.0	N.S.	78	Prostate	Adenocarcinoma	+	−	−	N.S.
37-A-190	♂	77	Larynx	Epidermoid carcinoma, grade II	+	−	−	0.6	N.S.	77	Prostate	Adenocarcinoma	+	−	−	N.S.
39-A-119	♂	77	Tongue	Epidermoid carcinoma, grade I	+	+	−	0.3	N.S.	77	Stomach	Adenocarcinoma	+	+	−	N.S.
42-A-10	♂	78	Larynx	Epidermoid carcinoma, grade II	+	−	−	1.0	N.S.	79	Prostate	Adenocarcinoma	+	−	−	N.S.
35-A-59	♂	79	Liver	Liver cell carcinoma	+	−	−	0.8	0.2	79	Sigmoid	Adenocarcinoma	+	−	−	0.6
39-A-36	♂	82	Thyroid	Carcinoma simplex	+	+	−	1.0	N.S.	83	Prostate	Adenocarcinoma	+	−	−	N.S.

TABLE VIII: CARCINOMA AND SARCOMA OF THE SAME ORGAN

Number	Sex	First cancer							Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
43-A-48	♂	54	Kidney, left	Renal cell adenocarcinoma	+	−	−	1.0	N.S.	54	Kidney, left	Rhabdomyosarcoma	+	−	−	N.S

TABLE IX: CARCINOMA AND SARCOMA OF THE SAME SYSTEM

Number	Sex	First cancer							Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
A-40-38	♀	46	Uterus	Adenocarcinoma	+	−	−	1.0	N.S.	47	Kidney, right	Myxoliposarcoma	+	−	−	N.S.
37,166	♂	61	Bladder	Myxosarcoma	−	−	−	1.5	N.S.	62	Kidney, left	Epidermoid carcinoma I	+	−	−	N.S.

TABLE X: CARCINOMA AND SARCOMA OF DIFFERENT SYSTEMS

Number	Sex	First cancer							Second cancer						
		Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration	Interval	Age	Organ	Lesion	Primary present	Metastases present	Metastases removed	Duration
33-A-148	♀	28	Breast, left	Carcinoma simplex	−	+	+	2.3	0.5	29	Mandible, right	Osteogenic sarcoma	+	−	−	1.8
37-A-113	♀	34	Lymph nodes	Hodgkin's disease	+	+	−	0.8	0.5	35	Breast, left	Carcinoma simplex	−	−	+	0.3
40-762	♀	43	Skin, nose	Basal-cell carcinoma	−	−	−	11.0	N.S.	54	Granulopoietic tissue	Myelogenous leukemia	+	+	−	N.S.
15,606	♀	50	Breast, right	Carcinoma simplex	+	+	−	2.3	N.S.	52	Uterus	Leiomyosarcoma	+	−	−	N.S.
19,392	♀	51	Breast, left	Carcinoma simplex	+	−	−	1.0	N.S.	51	Lymph nodes	Hodgkin's disease	+	+	−	N.S.
A-40-67	♂	55	Skin, nose	Basal-cell carcinoma	−	−	−	21.0	20.0	75	Lymphoid tissue	Lymphosarcoma	+	+	−	1.0
32,435	♀	57	Breast, left	Carcinoma simplex	−	−	−	13.0	9.0	66	Skin, arm	Hemangioendothelioma	−	+	−	4.0
39-A-30	♂	57	Bladder	Epidermoid carcinoma, grade III	−	−	−	1.0	0.5	58	Skin, N. S.	Malignant melanoma	+	+	−	5.0
40-A-21	♀	57	Thigh, subcutaneous tissue	Myxofibrosarcoma	−	−	−	5.0	4.5	62	Bladder	Undifferentiated carcinoma	+	−	−	0.5
35-A-14	♂	58	Skin, upper face	Epidermoid carcinoma, grade III	−	−	−	2.2	0.7	59	Lymphoid tissue	Lymphatic leukemia	+	+	−	1.5
38-A-47	♀	58	Breast, right	Adenofibrosarcoma	−	−	−	5.0	N.S.	63	Uterus	Leiomyosarcoma	+	−	−	N.S.
20,450	♀	61	Bronchus	Adenocarcinoma	+	+	−	1.1	N.S.	62	Uterus	Leiomyosarcoma	+	−	−	N.S.
36-A-121	♀	62	Granulopoietic tissue	Myelogenous leukemia	+	+	−	3.0	N.S.	65	Breast, left	Carcinoma simplex	+	+	−	N.S.
A 39-79	♂	63	Lymphoid tissue	Lymphosarcoma	+	+	−	1.0	0.8	64	Stomach	Adenocarcinoma	+	+	−	0.2
37-A-5	♀	66	Cervix	Epidermoid carcinoma, grade I	−	+	−	5.0	2.0	68	Skin, right ear	Malignant melanoma	−	−	−	3.0
34-A-78	♀	66	Tibia, left	Osteogenic sarcoma	+	−	−	0.5	N.S.	66	Kidney, left	Adenocarcinoma	+	−	−	N.S.
40,528	♂	67	Lymphoid tissue	Lymphatic leukemia	+	+	−	4.0	N.S.	71	Colon	Malignant adenoma	+	−	−	N.S.
37-A-57	♂	68	Pharynx	Undifferentiated carcinoma	+	−	−	0.5	0.0	68	Lymph nodes	Hodgkin's disease	+	+	−	0.5
42-A-47	♂	68	Bladder	Epidermoid carcinoma, undifferentiated	+	+	−	2.0	2.0	70	Granulopoietic tissue	Myelogenous leukemia	+	+	−	0.1
33-A-63	♂	68	Stomach	Lymphoma	+	+	−	0.5	N.S.	68	Liver, bile ducts	Carcinoma	+	−	−	N.S.
32-A-56	♀	70	Stomach	Adenocarcinoma	+	+	−	2.0	1.7	72	Lymphoid tissue	Lymphoma	+	+	−	0.3
45,972	♂	73	Granulopoietic tissue	Acute myelogenous leukemia	+	+	−	0.5	N.S.	73	Lung	Carcinoma simplex	+	−	−	N.S.
35-A-32	♂	76	Lymph nodes	Hodgkin's disease	+	+	−	0.7	N.S.	76	Pancreas	Adenocarcinoma	+	−	−	N.S.
40-A-22	♀	76	Cervix	Epidermoid carcinoma, grade II	+	+	−	0.2	0.0	76	Granulopoietic tissue	Acute myelogenous leukemia	+	+	−	0.2
41-A-89	♂	81	Antrum, left	Plasmocytoma	+	+	−	0.8	N.S.	82	Prostate	Adenocarcinoma	+	−	−	N.S.
41-2013	♂	81	Skin, foot	Malignant melanoma	−	−	−	6.0	4.0	85	Prostate	Carcinoma simplex	+	−	−	2.0
35-A-68	♀	82	Breast, left	Carcinoma simplex	+	−	−	2.0	1.8	84	Lymph nodes	Hodgkin's disease	+	+	−	0.2
46,272	♀	83	Peritoneum	Peritoneal sarcoma	+	+	−	0.2	N.S.	83	Colon	Adenocarcinoma	+	−	−	N.S.

instances complete. All diagnoses were based on histologic sections, and cases of malignant tumors removed prior to autopsy were not accepted unless the sections of such tumors were reviewed and the diagnosis confirmed. Only those tumors that unquestionably filled the generally accepted criteria for malignancy were considered. The criteria for multiplicity outlined by Warren and Gates (19) in 1932 were closely followed, namely: "Each of the tumors must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded."

Malignant tumors of the same organ or of symmetrical organs were included only if the clinical history and the gross and microscopic findings proved them to be independent. Thus only 6 cases of bilateral breast cancer were accepted out of a total of 10. All cases of bilateral ovarian malignant tumors were excluded because of the difficulty of differentiating between metastases and independent growths.

Teratomas were accepted only if there was microscopic evidence of malignancy. Primary intracranial tumors were excluded because of the difficulty in distinguishing between benign and malignant tumors in this locality. Furthermore, the brain was not examined in the majority of cases.

TABLE XI: SUMMARY OF TABLES I TO X

	Male		Female		Total
	Number	Average age	Number	Average age	
Table I: Cases of Four Malignant Tumors					
A. Skin	1	50.0	—	—	1
B. Miscellaneous	4	66.7	1	49.0	5
Total	5	63.4	1	49.0	6
Table II: Cases of Three Malignant Tumors					
A. Skin	—	—	1	67.0	1
B. Gastrointestinal tract (large intestine)	1	59.0	2	68.5	3
C. Miscellaneous	13	68.7	6	57.5	19
Total	14	68.1	9	61.0	23
Table III: Double Carcinomas of Same Organ					
A. Skin	3	78.7	—	—	3
B. Pharynx	1	74.0	—	—	1
C. Large intestine	12	62.0	4	62.5	16
Total	16	65.9	4	62.5	20
Table IV: Double Sarcomas					
A. Same system	1	35.0	1	60.0	2
B. Different systems	2	49.0	—	—	2
Total	3	44.3	1	60.0	4
Table V: Double Carcinomas of Symmetrical Organs					
A. Female breasts	—	—	5	50.4	5
Table VI: Double Carcinomas of Same System					
A. Gastrointestinal tract	8	61.8	1	76.0	9
B. Male genitourinary tract	5	71.6	—	—	5
C. Miscellaneous	1	70.0	—	—	1
Total	14	65.9	1	76.0	15
Table VII: Double Carcinomas of Different Systems					
A. Skin and gastrointestinal tract	7	63.4	—	—	7
B. Skin and genitourinary tract	4	75.3	1	55.0	5
C. Breast and skin	—	—	1	57.0	1
D. Breast and genitourinary tract	—	—	1	50.0	1
E. Breast and gastrointestinal tract	—	—	3	57.3	3
F. Genitourinary and gastrointestinal tracts	23	64.2	9	51.0	32
G. Miscellaneous	31	64.4	10	56.4	41
Total	65	65.0	25	54.3	90
Table VIII: Carcinoma and Sarcoma of Same Organ	1	54.0	—	—	1
Table IX: Carcinoma and Sarcoma of Same System	1	61.0	1	46.0	2
Table X: Carcinoma and Sarcoma of Different Systems	12	57.9	16	59.0	28
Grand Total	131	65.2	63	56.9	194

In order to facilitate comparison the data are presented in tabular form almost identical with that of the first series. However, slight changes and additions have been necessary since the present material does not fall into quite the same groupings as the previous material. Cases are arranged in order of increasing age. In the tables the age given for the time of development of each tumor is the age at onset of symptoms. When a precise past history was lacking the age at which the histologic diagnosis was first made is used.

This is at variance with the first series, in which the age at death was employed.

Duration is computed from the onset of symptoms of each tumor until death. Thus the difficult task of deciding when a tumor is "cured" is avoided. The interval, as given in the tables, represents the time between the onset of symptoms of successive tumors. In cases in which the malignant growth was found at autopsy but not suspected during life, the age given is that at time of death, and the interval and duration are reported as N.S. (not stated). Age, duration, and interval are recorded in terms of years.

vious group, probably owing to the use of age at time of death in the first series and age at onset of symptoms in the present series. The males average 65.2 years and the females 56.9 years. The considerable difference between the average ages of the male and female groups is identical in both series (9 years). The average age for the entire series is 62.5. The range in age is similar for the two groups: from 26 to 85 for the male group and from 28 to 83 for the female group.

The sex ratio in this series shows a preponderance of males (2.1:1) as against 1:1.6 in the first series. This is greater than one would expect from the male-

TABLE XII: INCIDENCE OF MULTIPLE MALIGNANT TUMORS REPORTED IN THE LAST 10 YEARS

Author	Total autopsies	Total cancer autopsies	Total cancer patients	Cases of multiple malignant tumors		Male-female
				Number	Percentage of cancer series	
Austin (1)	8124	887	—	24	2.7	—
Bugher (2)	4394	983	—	30	3.1	4 : 1
Burke (3)	2033	583	—	46	7.8	2 : 1
Cooper (4)	—	—	1790*	106	5.9	3.2 : 1
Desaive, Firket, Chevremont, and Dardenne (5)	—	—	3115	36	1.2	1 : 1.6
Gaudin (6)	—	—	4610	256	5.5	2.7 : 1
Hellendall (8)	—	685	—	30	4.3	—
Hurt and Broders (9)	—	—	2124	71	3.3	1 : 1.2
Kirshbaum and Shively (10)	10870	1411	—	25	1.2	2.2 : 1
Lund (12)	—	—	1548†	94	6.0	—
Phillips (14)	—	—	1400*	226	16.0	—
Schreiner and Wehr (16)	—	—	11212	307	2.7	—
Stalker, Phillips, and Pemberton (17)	—	—	2500	113	4.5	1 : 1.3
Tullis (18)	6836	1044	—	21	2.0	4.2 : 1
Warren and Gates (19)	—	1078	—	40	3.7	1 : 1.6
Warren and Gates (20)	—	—	1149*	237	20.6	—

* Cases of skin cancer.
† Cases of cancer of the mouth.

An attempt was made in all cases to determine whether metastases had been removed during life. The sign + indicates that histologically verified metastases were excised. Cases in which lymph nodes were removed but proved negative on microscopic examination, as well as those in which assumed metastases were treated by radiation, are recorded as "no metastases removed" (— sign). An asterisk indicates that at autopsy the metastases present could be attributed to one of or all the malignant tumors.

DISCUSSION

The data in this series show a parallel trend to the earlier study and accentuate its conclusions. We shall enumerate a few of the main points.

The average age is slightly lower than in the pre-

female ratio of the entire autopsy series (1.3:1). According to the Federal census of 1930 and that of 1940 the male-female ratio for the Massachusetts population over 25 years of age is 1:1.1. The slight preponderance of females in the general population would tend to lend further significance to the large proportion of males in the multiple malignant tumor series. The difference between the average ages of the male and female groups (9 years) may partly account for this. The male group, with a greater average age than the female group, would have had more time during which multiple tumors might develop.

Reports of multiple malignant growths based on autopsies (Table XII) generally show more males than females: Burke, 2:1; Tullis, 4.2:1; Kirshbaum and Shively, 2.2:1; Bugher, 4:1. However, some series

based on surgical material indicate a slight preponderance of females. Thus, Stalker, Phillips, and Pemberton found 1:1.3; Hurt and Broders 1:1.2; and Desaive and his associates 1:1.6. On the other hand, both Gaudin and Cooper noted a definite preponderance of males (2.7:1 and 3.2:1 respectively).

In view of the wide variation in sex distribution, it is doubtful that this factor is of consequence in the incidence of multiple malignancies.

The study of contrasted synchronous and metachronous tumors might provide an approach to the further elucidation of individual susceptibility to tumor development. Unfortunately, it is not always possible to be sure that such a distinction, which is of necessity based on clinical symptoms and biopsies, corresponds to reality. Furthermore, it is difficult to know how much significance to attach to the intervals between the development of tumors. In discussing synchronous and metachronous tumors, Warren and Gates (19) stated in 1932: "There is not much difference as far as information regarding heredity goes, and indeed regarding susceptibility as well, as to whether the patient develops his two tumors five years apart, ten years apart, or practically simultaneously."

Although we have recorded the interval between tumors when obtainable, and have indicated the tumors that we believed to be synchronous, our present data do not contribute anything new. The average interval between all tumors of the series is 3.1 years, that of all tumors except those of the cases of 3 and 4 malignant neoplasms is 3.2 years. The average interval between tumors in the cases of 3 and 4 malignant growths is 2.8 years. These figures are probably abnormally high since there are several intervals ranging between 10 and 20 years. Two years would probably be a more representative interval. Desaive and his coworkers (5) found an average interval of 1.8 years in their group.

It has been suggested that multiple malignant tumors constitute an indirect measure of the degree of intensity of malignancy or of the disposition to cancer in an individual. The study of survival rates provides an approach to this relationship. Multiple malignant growths in themselves do not alter survival rates to any appreciable degree. The average duration of life for the entire series, reckoned from the onset of symptoms of the first tumor, is 2.7 years. This is close to that of the previous series and subject to the same reservations, since 2 cases of 20 and 21 years' duration respectively, and 8 cases between 10 and 20 years bring up the average appreciably. The average duration of the cases of 3 and 4 malignant growths is 4.7 years, although this figure is too high, since there are cases of 21, 15, and 11 years' duration. It gives further ground for the assumption that the presence of numerous malignant tumors does not necessarily imply a worse prognosis. It seems unlikely that the degree of malignancy is related to multiplicity.

On Table XIII is plotted the encounter of tumors of the various organs in the 194 cases of multiple malignant growths. No distinction is made here between carcinoma and sarcoma. Inasmuch as it was difficult to record all the tumors of Tables I and II (cases of 4 and 3 tumors, respectively), only the first two in these cases were included. This table brings out the relatively large number (36, or 18.6 per cent) of multiple tumors in the same organ (including breasts). The association of the breast and gastrointestinal tract is about equal to that of the breast and genital tract. Although neoplasms of the large intestine are frequently associated with tumors derived from other parts of the gastrointestinal tract, association with growths of other organs is almost as frequent. Tumors of the prostate are associated with a wide variety of growths by no means limited to the genitourinary tract, or even to glandular epithelium. About half of the neoplasms of the female genitourinary tract are associated with others arising from glandular epithelium common to both sexes.

Thus although there is some evidence that organ or tissue specificity with regard to the development of tumors may exist, the evidence provided by this series is not conclusive. Conversely, there is nothing that suggests an antagonism between tumors derived from different organs or tissue.

On the basis of all the tumors, the organs most frequently involved in the group of 194 multiple tumors are:

Colon	with	95	malignant	tumors	in	69	patients
Skin	"	44	"	"	"	34	"
Pharynx *	"	34	"	"	"	30	"
Stomach	"	28	"	"	"	28	"
Uterus (including cervix)	"	23	"	"	"	22	"

* This includes buccal cavity and pharynx.

Almost all studies of multiple malignant neoplasms show a high proportion of multiple cancers of the gastrointestinal tract. These are chiefly of the large bowel and may be related to polyposis, in which secondary malignant changes are so common. A summary of the cases with large bowel involvement may be found in Table XIV. In one-third of the cases of carcinomas of the large bowel there was a second carcinoma in this location. In 9 cases a tumor of the large bowel was associated with one in another part of the gastrointestinal tract. In 31 cases there was a tumor of the gastrointestinal tract elsewhere than in the large bowel, chiefly in the stomach.

It is interesting to note that the average age is no lower in the cases of multiple carcinomas than in cases of single carcinoma of the colon. Polyposis, often congenital, familial (21), and predisposing to cancer, no symptoms during life. Since many are in the older age groups, one might contend that the inclusion of these cases in the series gives a false impression of the clinical significance of multiple malignant neoplasms.

TABLE XIII: CONCURRENCE OF MULTIPLE MALIGNANT TUMORS *

	SKIN	BREAST	PHARYNX	PAROTID	THYROID	LARYNX	LUNG	ESOPHAGUS	STOMACH	SMALL INTESTINE	LARGE INTESTINE	LIVER	PANCREAS	ADRENAL	KIDNEY	BLADDER	PROSTATE	TESTIS	OVARY	UTERUS	CERVIX	BONE	GRANULOPOIETIC TISSUE	LYMPHOID TISSUE	LYMPH NODE	SUBCUTANEOUS TISSUE	PERITONEUM	NERVE
SKIN	5																											
BREAST	2	6																										
PHARYNX	6		2																									
PAROTID																												
THYROID		1																										
LARYNX																												
LUNG	1					1																						
ESOPHAGUS	1		2		1																							
STOMACH	2	1	5				1	1																				
SMALL INTESTINE		1																										
LARGE INTESTINE	4	2	2	1		1	2	1	6	1	20																	
LIVER		1							1		1																	
PANCREAS		2	1			1					1																	
ADRENAL																												
KIDNEY			2						1						1													
BLADDER	2		2						1		2				1													
PROSTATE	5		7		1	4	1	4	4		13	1	1		2	3												
TESTIS														1														
OVARY											3																	
UTERUS		2			1		1		1		2				1				2	1								
CERVIX	1	1							1		3	2							1									
BONE		1													1		1					1						
GRANULOPOIETIC TISSUE	1	1					1									1					1							
LYMPHOID TISSUE	4								2		1																	
LYMPH NODE		3	1										1										1					
SUBCUTANEOUS TISSUE																1												
PERITONEUM											1																	
NERVE																							1					

* Only the first 2 tumors of Tables I and II are included.

TABLE XIV: TUMORS OF THE LARGE BOWEL

	Two or more malignant tumors			One malignant tumor		
	Male	Female	Total	Male	Female	Total
Number	17	6	23	35	11	46
Age range	42–78	52–75	42–78	26–79	27–83	26–83
Average age	62.6	64.5	63.1	64.5	56.2	62.5

is too rare to affect these statistics. The predominant male-female ratio is characteristic of carcinoma of the bowel and it is in keeping with the series.

Carcinoma of the prostate constitutes another large group. Some of these were found at autopsy and gave However, on analyzing the 52 cases in which there was a carcinoma of the prostate, one gets a different picture. Seven cases gave symptoms during life; 8 are in groups of 3 or more malignant tumors and would therefore be included in the series even if the

prostatic tumor were absent. Of the remaining 37, there are 8 in the 50 to 59 age group, in which it is reasonable to assume that the malignant prostatic growth would have given symptoms had the patient lived. We are thus left with 29 cases ranging between 60 and 90 years of age. Even if this group were excluded from the total series, the incidence of multiple malignant neoplasms would still be high (5.8 per cent instead of 6.8 per cent).

The groups of 3 and 4 primary malignant tumors constitute respectively 12 per cent and 3 per cent of the total group. This is roughly the same as the incidence of similar cases in the group collected from the literature by Warren and Gates (19). In that group the number of multiple skin cancers accounted for about one-third of the cases of 3 or more malignant growths; whereas in our present series there are 2 cases with 3 cancers of the skin (one of these is associated with a fourth tumor of a different organ) and one case of 4 cutaneous cancers. The relatively small number of multiple skin tumors in this series is probably attributable to omissions on the part of patients when giving their past history, and to the treatment of some skin lesions without biopsy.

The significance of the data on the relative frequency with which certain organs were involved depends on the sample analyzed. It is difficult to avoid a certain amount of selection of cases. Our 2,829 cases were derived from 3 hospitals of different types. The majority came from Pondville State Hospital and Westfield State Sanatorium, which tend to have a larger proportion of terminal-care patients in the older age groups. A large proportion of cases of carcinoma of prostate are in the Pondville group. The majority of cases from the C. P. Huntington Memorial Hospital were lymphomas and leukemias. The patients from the New England Deaconess Hospital were for the most part private and represent a different social stratum. Remote data on these patients were less easily verified. Also, the majority of deaths were postoperative or followed acute illness unrelated to cancer. For these reasons, comparisons of the frequency with which certain organs are involved in the main sample and in the group with multiple tumors may be of interest in judging the susceptibility to cancer of certain organs as represented in the group of cases of primary multiple tumors. In Table XV we have listed the organs most often involved.

By comparing the organs affected in the series of multiple malignant growths, and the distribution of tumors in the series as a whole (Table XV), it is clear that there is no constant ratio between organs involved in the series of one cancer and the series with 2 or more cancers, with exception of the large intestine. Although there are more than twice as many cancers of the stomach as skin in the group of single tumors, those organs are affected with equal frequency in the group of multiple cancers. Also there are more cancers of the cervix than of the stomach in the group of single tumors and only half as many in the group of multiples.

"Collision" of tumors or of metastases is infrequent. Among the 194 cases in which there was a total of 423 malignant tumors (of these 285 were present at death), 162 cancers had metastasized. There were only 3 instances of "collision tumor." These 3 cases deserve special mention since each exemplifies a variety of collision tumor, *i.e.*, the encounter of 2 malignant

TABLE XV: DISTRIBUTION OF CASES BY SITE

Organ	Entire autopsy series		Multiple malignant autopsies	
	Number	Per cent	Number	Per cent
Large intestine	476	16.9	69	35.6
Uterus (including cervix)	311	11.0	22	11.3
Stomach	243	8.6	27	13.9
Pharynx	242	8.6	31	16.0
Breast	237	8.4	25	12.9
Lymph node	158	5.6	11	5.7
Prostate	135	4.8	52	26.8
Skin	131	4.6	34	17.5
Bladder	125	4.4	14	7.2
Lung	120	4.3	9	4.6
Leukemia	97	3.4	11	5.7
Esophagus	83	2.9	12	6.2

tumors or their metastases. Case 43-A-48 (Table VIII) presented the encounter of 2 primary malignant growths in their site of origin: a renal cell adenocarcinoma and a rhabdomyosarcoma, both arising in the left kidney. In case 38-A-11 (Table VII, F.) an epidermoid carcinoma of the bladder metastasized to a mucinous carcinoma of the rectum. In case 19,862 (Table II, C.) there was collision between the lung metastases of a carcinoma simplex of the breast and an adenocarcinoma of the pancreas.

The coexistence of multiple malignant tumors and benign tumors has been noted by many authors, but statistical data are not readily available. Although no attempt was made to determine the incidence of benign growths in this series, it was noted that a number of cases showed a striking number of benign tumors involving several organs and systems. Case 60,431 (Table II, C.) provides a good illustration. The patient, who was 58 years of age at the time of her death, had 3 malignant neoplasms (leiomyosarcoma of uterus with lung metastases, adenocarcinoma of ovary with numerous metastases, and lymphatic leukemia), and 5 benign tumors (adenoma of islet of Langerhans, Hürthle-cell adenoma of thyroid, leiomyoma of stomach, embryonal cyst of kidney, and hemangioma of lip).

In 1932 Wilson and Maher (22) discussed the statistical significance of the occurrence of multiple malignant growths and estimated the expected incidence to be 5 to 6 per thousand (based on the Massachusetts mortality rates for 1902, 1912, and 1920-1927, prepared by Dr. H. L. Lombard). In analyzing the first series, Warren and Gates (19) used a table set up by Dr. Lombard and centering at the same year as the cancer autopsy series. The expected number of multiple malignant neoplasms in the series of 1,058 cancer autopsies, on the basis of 2 years' duration, was 10.5, whereas the actual number observed was 40.

Desaive and his co-workers (5) based their statistical studies on the population of Liége, Belgium, from 1925 to 1934. The expected incidence of multiple malignant growths was calculated to be 6 per thousand. It is noteworthy that, working with two entirely different population samples, Wilson and Desaive found almost identical figures (5 to 6, and 6 per thousand, respectively).

In the present series the observed incidence of multiple malignant tumors is 68 per thousand; on the basis of both series it is 60 per thousand. The expected incidence of multiple malignant neoplasms in our present series is 17; the observed incidence is 194, or eleven times the number expected if chance alone were a factor. This is a further confirmation of the existence in some persons of a susceptibility or predisposition to cancer.

SUMMARY

1. In a series of 2,829 cancer autopsies, 194 cases of multiple malignant neoplasms were encountered, an incidence of 6.8 per cent. Together with the series previously reported there are 3,907 autopsies with an incidence of 6.0 per cent multiple cancers.

2. In the group of 194 patients with multiple malignant tumors there are 131 males and 63 females.

3. The average age of the male group is 65.2 years, of the female group, 56.9 years, and of the entire group 62.5 years.

4. The average duration from onset of the first tumor until death is 2.7 years.

5. The average interval between successive tumors, when it could be determined, is 3.1 years.

6. Cases of multiple malignant growths occur more frequently than the expected incidence based on chance alone.

7. This greater frequency, calculated as elevenfold, may be attributed to susceptibility or predisposition to cancer in some persons or groups of persons.

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Cancer of the Liver in the Negro in Africa and in America*

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CONTENTS

Cancer of the Liver in the Negro in Africa

Berman [1] (2-5) has drawn attention to the prevalence of primary cancer of the liver among the Bantu of South Africa. His material was drawn largely from the native hospitals of the Witwatersrand Gold Mines, which treat annually about 67,000 patients from a total Bantu population of about "200,000 specially selected and fit young male adults whose ages ranged between 28 and 45 years, the average being about 30 years. This negro population was examined twice and often three times before being accepted as physically fit for employment. . . . They constitute a shifting population rarely remaining on the mines longer than nine months at a stretch, during which period they scarcely have the opportunity to establish close contact with civilized life. While in residence in the mine compounds, they are encouraged to maintain their native customs and habits and their rural characteristics. . . . During the years 1925 to 1933, 253 cases of carcinoma were recorded amongst the Bantu labourers. 229 (or 90.5 per cent) were primary liver cancers."

Berman's collection (2) from 16 other authors of data for Bantu in the Union of South Africa, Portuguese East Africa, Kenya, Tanganyika, Belgian Congo, Fernando Po, and French Equatorial Africa shows a lower, but still very high, figure for this percentage, namely 37.4. If this proportion of primary cancers of the liver occurred in any large white population the disease would be held to constitute a major problem of cancer research; as it is, the subject seems to have attracted little attention from investigators.

The prevalence of cancer of the liver among Bantu might be due to (a) environmental, or (b) genetic, factors and there might, of course, be a genetic susceptibility to an environmental factor. Theoretically, the obvious experiment is to cause a white population to adopt the Bantu mode of life; as this is impossible, one must seek for less direct evidence.

Berman (2) has collected the available data on the prevalence of primary cancer of the liver all over the world. Roughly, the area of high incidence extends from the West Coast over the southern half of Africa and across southern and southeastern Asia, including Sumatra, Java, and the Philippines, to China and Japan. One cannot expect that any genetic factor of the kind in question is common to the people of the west coast of Africa, and of China, and it is not much easier to think of any common external factor.[2]

* Because of the difficulties of international communication the author has not read proof of this article.

[1] These papers have been abstracted in *Cancer Research* (**1**:176, 177, 915, 941; **2**:591. 1942).

[2] The consumption of the various kinds of millet suggests itself as a factor common to many of the countries in question, but Kinosita (20) states that cancer of the liver is less common among the northern millet-eating people of China than among the southern rice-eating people. No attempt is made here to enumerate possible etiological factors: see Berman (5).

The Negroes of America offer an opportunity to obtain evidence on this question, as they are removed from the environmental factors of Africa. They are of course derived, not from the Southern Bantu of South Africa, who are admixed to a varying extent with races from the north who have moved down the eastern side of Africa, and with the Bushmen and other peoples, but from the true Negroes of West Africa (Seligman 38). Berman has collected the few available data for the incidence of cancer of the liver upon West African Negroes (of Senegal, Sierra Leone, and Nigeria), and finds that this form of cancer makes up 18.7 per cent of all cancers recorded. This is a lower proportion than that shown by the southern Bantu, but is still very much higher than that found among Europeans (of Britain, Holland, Switzerland, and Germany), among whom the corresponding figure is 1.1 per cent. One must inquire, then, whether Europeans and West Africans, when transferred to America, maintain this difference. Some authors have concluded that primary carcinoma of the liver in man is controlled by racial and not by environmental factors, and that Negroes in Amercia show the same tendency to it as do those in Africa.

Cancer of the Liver in the Negro in the United States

The evidence on this subject consists of (a) statistical data, and (b) records of individual cases. In the following sections the terminology of each author in regard to "Liver and Gall Bladder"; "Liver, Gall Bladder, and Gall Ducts"; and "Liver and Biliary Passages" has been followed exactly; presumably the last of these includes the gall bladder.

(a) *Statistical evidence.*—Apparently no data are available on the number of cases of cancer of the liver, excluding cancers of the gall bladder and bile passages, in the United States. Government departments naturally tend to pool different forms of cancer in order to reduce the number of groups, and this pooling is done on the basis of anatomical proximity. Thus, before 1923, the Registrar-General's figures for deaths from cancer in England and Wales combined cancers of the penis and scrotum in one group although the two organs are subject to very different etiological factors. Cancer of the gall bladder is more common in women, and hence the inclusion of cancers of the liver and gall bladder in one group confuses the matter. Berman (4) makes no mention of the occurrence of cancer of the gall bladder among the Bantu. Of his 25 cases of primary carcinoma of the liver, 24 were hepatocellular and one was a cholangioma.

The greater incidence of cancer of the gall bladder upon women is illustrated by the Registrar-General's figures (32) for England and Wales in Table I.

Table I: Cancer of the Gall Bladder
England and Wales

	Cancer of the gall bladder, mortality rates per million population (standardized)	
	Men	Women
1911-1920	6.0	11.6
1921-1930	8.8	16.6
1931	9.2	16.9
1932	10.8	16.9
1933	9.6	16.5
1934	8.5	17.0
1935	9.3	16.6

Dublin and Lotka (10), when comparing the death rates shown by 19,670 deaths from cancer of the liver and gall bladder in white and colored policyholders of the Metropolitan Life Insurance Company between 1917 and 1935, found that "Malignant tumors of the liver and gall bladder showed a definitely higher rate for the whites in each sex" (Table II).

Table II: Cancer of the Liver and Gall Bladder

Averages of Annual Death Rates, By Color, Sex, and Age. Ages 25 to 74 Years

Metropolitan Life Insurance Company, Industrial Department, 1917 to 1935

Average period, years	Average of death rates per 100,000 White		Colored	
	Males	Females	Males	Females
1 to 74 *	6.5	9.0	4.1	4.9
45 " 74 *	31.2	43.3	19.2	21.7
25 " 34	0.5	0.8	0.6	1.0
35 " 44	3.0	4.7	2.5	4.6
45 " 54	12.9	18.1	10.8	11.4
55 " 64	37.4	49.5	22.1	25.4
65 " 74	69.3	99.9	36.6	42.8

* Death rates standardized for age.

Pearl and Bacon (29), in a study of 816 autopsies upon cases of malignant tumor at Johns Hopkins Hospital during the years 1889 to 1923, give the following data obtained from this material (Table III).

Table III: Carcinomas of Liver, Gall Bladder, and Gall Ducts

Johns Hopkins Hospital

(Pearl and Bacon)

White males		Colored males		White females		Colored females	
Absolute	Per cent *	Absolute	Per cent	Absolute	Per cent	Absolute	Per cent
9	4.5	6	10.5	23	30.3	2	12.5

* Per cent = percentage of all carcinomas of the alimentary tract, liver, and pancreas.

The figures suggest a higher incidence of these tumors upon colored than upon white males, but the numbers are not large enough to be decisive and the proportion of gall-bladder tumors is unknown; otherwise these data would have been of especial value as the proportion of white (58.6 per cent) and colored (41.4 per cent) in the whole series of 6,670 autopsies used was not very different.

Dr. Louis I. Dublin has very kindly supplied me with the material based on data from the United States Bureau of the Census, that is contained in Tables IV and V. Table IV shows the numbers of deaths,

TABLE IV: NUMBER OF DEATHS AND THE DEATH RATES PER 100,000 POPULATION FROM CANCER OF THE LIVER AND BILIARY PASSAGES BY COLOR AND AGE GROUPS FOR THE UNITED STATES, 1938. BASED ON DATA FROM THE UNITED STATES BUREAU OF THE CENSUS

	White		Colored	
Age groups	Deaths	Death rates	Deaths	Death rates
Under 25	67	.13	4	.06
25 to 34	80	.43	24	1.03
35 " 44	374	2.34	60	3.42
45 " 54	1,214	8.79	129	9.76
55 " 64	2,344	24.40	150	17.87
65 " 74	3,125	59.10	130	38.55
75 and over	2,306	105.44	59	41.49

and the death rates, from cancer of the liver and biliary passages among whites and colored at various age periods. At the earlier ages the mortality is higher among the colored, but from the age of 55 onwards the incidence becomes considerably higher upon the whites.

Table V shows the crude death rates for each state from cancer of all forms, and from cancer of the liver and biliary passages, with the percentage ratio of these two quantities to one another, arranged in descending order of this last amount; and to these data I have added the percentage of Negroes in the population of each state shown by the census of 1940 (40). In all the states together, cancers of the liver and biliary passages make up 6.8 per cent of all cancers. If one takes the 20 states in which this percentage is highest, ranging from 7.7 in Texas to 10.8 in South Dakota, and outlines them upon a map, one obtains the result shown in Fig. 1. Maine is altogether aberrant; otherwise the states form a continuous area, which avoids the northern border and the east and west coasts. If one outlines also upon the map the 14 states having more than 10 per cent of Negroes, who in these states number 9,403,985, or 73 per cent of the total in all the states, it is quite obvious that the two areas do not coincide. The data in the graph (Fig. 2) show that there is an abrupt transition from the 34 states having less than the mean proportion (9.8 per cent) of colored persons to the 14 states having more than this amount. This abruptness is, from the present point of view, fortunate, because it should make more conspicuous any difference between the two groups of states that depends upon this proportion. Hence these data give no indication that there is any high

TABLE V.—DISTRIBUTION OF CANCER OF THE LIVER AND BILIARY PASSAGES AND OF NEGROES, IN THE UNITED STATES

	Death rates per 100,000, 1938			
State	Cancer, all forms A	Cancer of Liver and Biliary Passages B	B, per cent of A	Negroes, per cent of population, 1940
South Dakota	92.3	10.0	10.8	0.1
Indiana	122.6	12.8	10.4	3.5
Kentucky	81.2	8.2	10.1	7.5
Virginia	84.4	7.9	9.4	24.7
Arizona	72.3	6.8	9.4	2.6
West Virginia	75.6	7.0	9.3	6.4
Oklahoma	75.1	7.0	9.3	7.2
Nevada	121.7	11.3	9.3	0.6
Mississippi	65.1	5.9	9.1	49.2
Idaho	89.2	7.9	8.9	0.1
Maine	153.9	13.5	8.8	0.1
Nebraska	122.8	10.5	8.6	1.1
New Mexico	55.4	4.7	8.5	0.9
Kansas	123.0	10.2	8.3	3.6
Missouri	131.7	10.9	8.3	6.4
Ohio	129.3	10.6	8.2	4.9
Tennessee	75.6	6.2	8.2	17.4
Iowa	132.9	10.5	7.9	0.7
Arkansas	58.8	4.6	7.8	24.7
Texas	72.8	5.6	7.7	14.4
New Hampshire	162.1	12.2	7.5	0.1
South Carolina	54.9	4.0	7.3	42.8
Utah	85.2	6.1	7.2	0.1
North Carolina	54.8	3.9	7.1	27.4
Delaware	120.5	8.5	7.1	13.4
Vermont	143.3	10.1	7.0	0.1
North Dakota	96.9	6.6	6.8	0.1
Montana	101.3	6.9	6.8	0.2
Maryland	128.4	8.7	6.8	16.5
Michigan	112.6	7.6	6.7	4.0
Wisconsin	132.7	8.7	6.6	0.4
Pennsylvania	125.9	8.3	6.6	4.7
Oregon	140.2	9.3	6.6	1.9
Colorado	115.4	7.4	6.4	1.1
Illinois	138.2	8.9	6.4	4.9
Washington	135.1	8.7	6.4	0.4
Alabama	60.3	3.8	6.3	34.6
Florida	85.8	5.2	6.1	27.0
Rhode Island	153.0	9.2	6.0	1.5
Georgia	63.8	3.8	6.0	34.7
Louisiana	81.6	4.8	5.9	35.9
California	136.8	8.1	5.9	2.2
New Jersey	134.7	8.0	5.9	5.4
Massachusetts	161.2	8.1	5.0	1.2
New York	153.4	7.7	5.0	4.2
District of Columbia	139.6	6.7	4.8	28.2
Minnesota	135.7	6.3	4.6	0.3
Connecticut	146.0	6.1	4.2	1.9
Wyoming	87.2	3.3	3.8	0.4
United States	115.0	7.8	6.8	9.8

incidence of cancer of the liver upon the Negro in America. The ratio B:A (Table V), which suggests this conclusion, is of course an unsatisfactory basis, because it may be altered by the prevalence of any form of cancer included in A; but any such preponderance of cancer of the liver as occurs in South Africa could not be concealed.

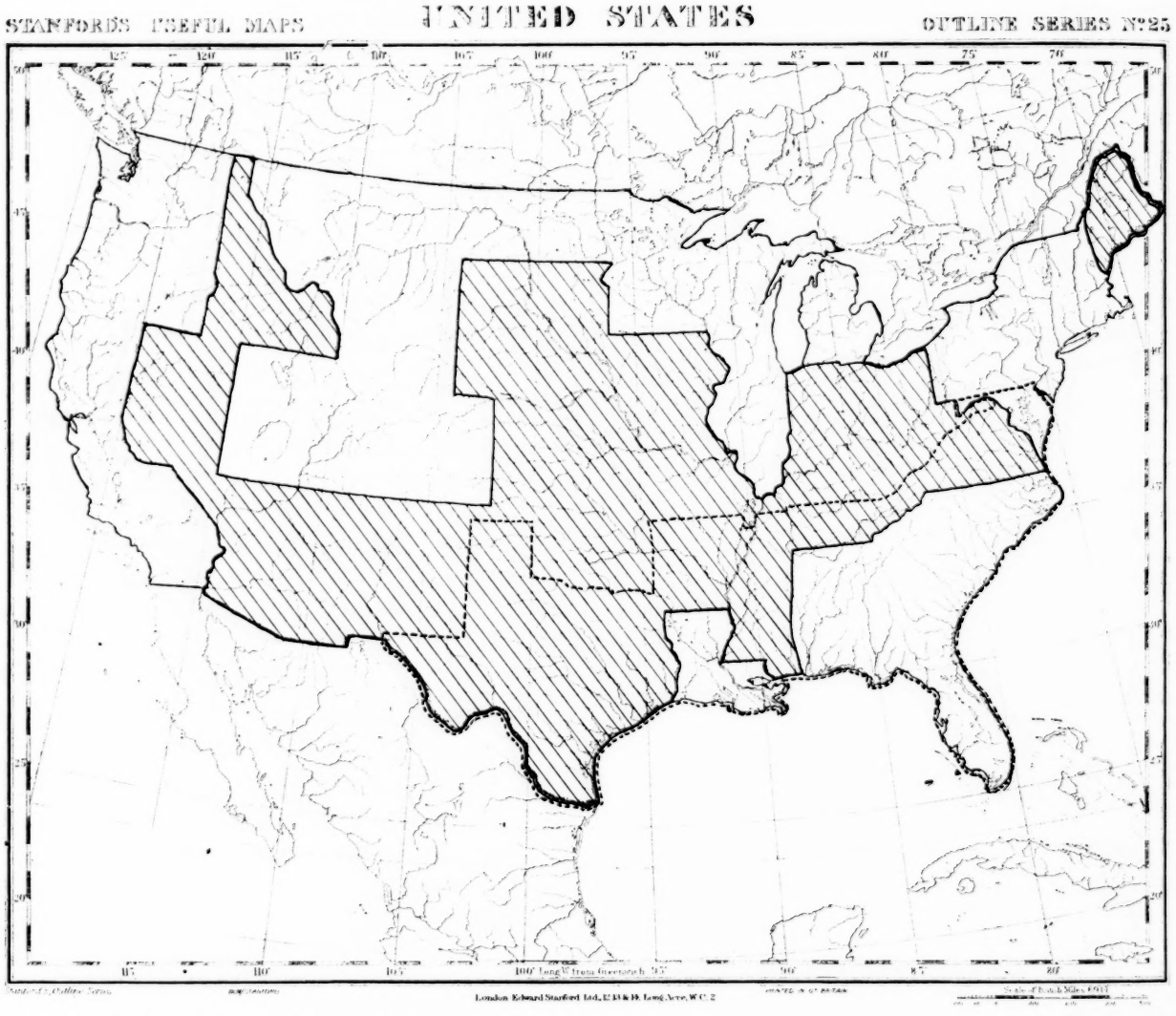

FIG. 1.—The broken line encloses the 14 states in which Negroes make up more than 10 per cent of the population (Fig. 2). The cross-hatched areas show the 20 states in which the proportion of cancers of the liver and biliary passages is highest (Table V).

The mean ratio of cancers of the liver and biliary passages to all cancers is higher in the United States, 6.8 per cent, than in England and Wales, 5.18 per cent in 1933-1937 (32). One factor that would raise this figure is the recording of metastatic tumors of the liver as primary tumors in thinly populated areas where the conditions for diagnosis are not good, and these conditions are difficult to assess numerically. The 20 states outlined in Fig. 1, in which most deaths are ascribed to cancer of the liver and biliary passages, contain 46,116,632 inhabitants in 1,475,763 square miles; this is a mean density of 31.25 persons to the square mile, which is less than three-quarters of the density for the whole of the United States, namely 44.2. But there is no simple relation to population density; thus the 2 states at the top of Table V are South Dakota (density 8.4 persons per square mile) and Indiana (density 94.7).

(b) *Individual cases of primary carcinoma of the liver.*—Statistics based upon attendance at hospitals are notoriously liable to many errors. Table VI summarizes the relevant data for 233 cases of primary cancer of the liver occurring in the United States and published since 1911; this does not claim to be a complete collection of the cases reported. Where no statement was made about race the patient has been assumed to be white; in some cases, where the race is not stated, one can infer from the details of the clinical description devoted to the patient's complexion that

TABLE VI: CASES OF PRIMARY CARCINOMA OF THE LIVER IN THE UNITED STATES, CLASSIFIED ACCORDING TO RACE AND SEX

Author	Institution or locality	White			Colored			Other races	Race not stated	
		Male	Female	Sex not stated	Male	Female	Sex not stated		Male	Female
Barry and Russum	Creighton University, Omaha, Nebr.	4								
Brines	Detroit Receiving Hospital, Detroit, Mich.	6	1		1					
Charache	Brooklyn, N. Y.							Philippine male		
Clawson and Cabot	University of Minnesota Medical School, Minneapolis, Minn.	1								
Counseller and McIndoe	Mayo Foundation, Rochester, Minn.								5	
Fox and Bartels	State University of Iowa, Iowa City, Iowa								2	1
Fried	Harvard University and Peter Bent Brigham Hospital, Boston, Mass.	1								4
Friedenwald and Fried	University of Maryland, Baltimore, Md.		1							
von Glahn and Lamb	Presbyterian Hospital, New York, N. Y.	3						Chinese male		
Gnassi	Medical Center, Jersey City, N. J.	3				1				
Gregory	Washington, D. C.				1					
Gustafson	Bellevue Hospital, New York, N. Y.			53			4	4 Chinese 1 Japanese ? sex		
Jenks, Powell, and Kaump	Methodist Hospital, Des Moines, Iowa							Philippine male		
Karsner	Philadelphia, Pa.	6	2					Chinese male		
Levitt and Levy	Buffalo City Hospital, Buffalo, N. Y.*								15	1
Liber and Brown	Lincoln Hospital, New York, N. Y.		1							
Lisa and Hart	City Hospital, Welfare Island, N. Y.			8			4			
Loesch	Buffalo City Hospital, Buffalo, N. Y.*	12	2							
Mast and Streamer	Pueblo, Colo.	1								
McIndoe and Counseller	Mayo Foundation, Rochester, Minn.									1
Mallory	Massachusetts General Hospital, Boston, Mass.	1	1							
Peller and Stephenson	United States Navy	21			2			6 male (Philippine, Chinese, Japanese)		
Quinland and Cuff	Meharry Medical College, Nashville, Tenn.				2	1†				
Robertson, Robertson, and Bower	Philadelphia General Hospital, Philadelphia, Pa.	1								
Rowen and Mallory	Boston City Hospital, Boston, Mass.	1							8	1
Sanes and MacCallum	Buffalo General Hospital, Buffalo, N. Y.	1	1							
Saward	Peter Bent Brigham Hospital, Boston, Mass.	1								
Schnabel	Philadelphia General Hospital, Philadelphia, Pa.							Chinese male		
Smith	University of Illinois, Chicago, Ill.	19	2		4					
Wallace	Pondville Hospital, Norfolk, Mass.		1							
Winternitz	Johns Hopkins Hospital, Baltimore, Md.	1			3					
	TOTAL	83	12	61	13	2	8	16	30	8
		156			23				38	

* I have been unable to ascertain whether these two reports from the same hospital deal to any extent with the same cases.

† There was also an "adenocarcinoma of bile duct origin, in a woman aged 44".

the person was not colored. Cases occurring in infancy have been excluded as probably of a special nature. Only 2 cases of the 23 in colored persons can be said definitely to have been women; some authors state the numbers of white and colored patients, and the numbers of men and women, but do not state the sex in relation to race. The locality where each investigation was carried out is recorded, as this of course affects the racial character of the population concerned.

The table shows 184 cases in persons white, or assumed to be white, and 23 cases in Negroes, which is a ratio of 8 white to 1 colored. This is not very different from the ratio of the two populations. The census of 1940 (40) gave 118,214,870 whites to

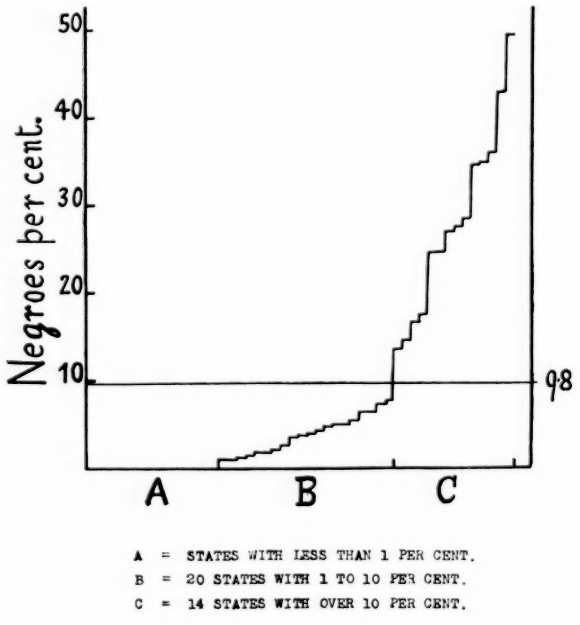

FIG. 2.—Proportion of Negroes in the population of the United States. The states are arranged from left to right in ascending order of the percentage of Negroes. The horizontal line indicates the mean percentage (9.8) in the whole population.

12,865,518 Negroes, or 9.2 white to 1 colored. At first sight, therefore, the published cases indicate that the incidence of this form of cancer upon the two races is the same. But in view of the very small proportion of colored persons in many of the localities (Table V and Figs. 1 and 2) named in the second column of Table VI, the figures might be held to suggest that they were especially liable to cancer of the liver. Evidently, unless the people of the South are to a high degree exempt from this form of cancer, many cases among them must go unrecorded. The likelihood of publication is a factor that cannot be estimated numerically. (The number of cases in the small population of Chinese [74,954 in 1930] presents an altogether different problem, as some of them, at any rate, are immigrants who have spent their early life in China. Strong and Pitts [41, 42], at Vancouver General Hospital, record 10 cases in 139 autopsies on Chinese, who are mostly immigrants from Kwangtung province in southern China. Data on the incidence of cancer of the liver upon Chinese born in America would be very desirable.)

DISCUSSION

The suggestions in this paper are put forward with diffidence, in the hope that American workers who are in a position to obtain firsthand information will be attracted by this question. The data collected above give no definite indication that the Negro in America shows the high incidence of primary cancers of the liver that is found in Africa, and hence the prevalence of this form of cancer in Africa does not appear to depend purely on racial characters. But all statistics on this matter are defective as long as cancers of the gall bladder, and of the liver, are included in one category; primary cancer of the liver is at the best a bad subject for mass statistics, on account of the danger of inclusion of metastases from undetected primary tumors elsewhere. The experimental work of the last 12 years has shown both how easily cancer of the liver is induced in the rat and mouse by certain compounds given with the food, and the controlling influence of diet upon this process. The presence of similar compounds in some of the numerous foodstuffs of Africa, of the constituents of which we have very little knowledge, is quite possible. Berman gives a valuable piece of information upon this matter, but does not draw any inference from it. Among the natives who come to the gold mines from Portuguese East Africa cancer of the liver is about 6 times more common than it is among those from other areas. Since these natives show no special racial peculiarities (Berman says "There is no appreciable difference in their general physical characteristics") some local environmental factor is indicated.

SUMMARY

Such data as are available suggest that the very high incidence of primary cancer of the liver found among Negroes in Africa does not appear among Negroes in the United States, and is therefore not of a purely racial character. Hence the prevalence of this form of cancer in Africa may be due to some extrinsic factor, which could be identified. The statistical evidence on this question is confused by the inclusion of cancer of the gall bladder in the same category with cancer of the liver.

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Observations on Mouse Tumors Cultivated in the Yolk Sac of the Embryonic Chick

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In 1926 Murphy (13) reported successful cultivation of the Jensen rat sarcoma on the chorio-allantois of the chick embryo and subsequent transplantation of the "egg" tumors to rats. The tumors were carried for 4 serial passages in eggs before being lost. The survival time of the tumor cells was tested by inoculation into adult or newly hatched chickens. It was found that, while the cells of tumors from rats would survive for 3 days under these conditions, those of the tumors grown in eggs disappeared completely within 24 hours. Because of this fact, Murphy concluded that the cells of the Jensen sarcoma appeared to have become less resistant during their growth in the egg.

Taylor and his co-workers (18, 20) recently described the successful cultivation of mouse tumors in the yolk sac of the chick embryo. Taylor later reported the presence of a cell-free agent in the yolk surrounding such tumors that caused the rapid production of tumors when inoculated into mice (17).

One of us (11), using the technic described by Taylor and his associates, observed that a mammary carcinoma from a mouse of the inbred C3H strain would grow in the chick embryo, and that these tumors could be transplanted to mice of the parental stock.

MATERIAL AND METHODS

Spontaneous mammary carcinomas originating in mice of the C3H or the A strain were used in this study. Histologic sections showed them to be highly undifferentiated tumors typical of those originating in these strains of mice.

The method of yolk-sac cultivation was essentially that described by Taylor and his group (18). In the present study, however, the inoculum was prepared under a hood by grinding the tumor in a mortar together with a physiologic solution of sodium chloride. In most cases the tumor material was weighed and a 40 per cent suspension prepared for inoculation, though occasionally the material was not weighed and a 40 per cent suspension was approximated. Two-tenths cubic centimeter of this suspension was then inoculated into the yolk sac of the 5-day chick embryo. Previous experiments had shown that considerable variation in the size of the inoculum made no difference in the growth of the tumors. All the inoculations were performed by the same worker. With a few exceptions, the inoculated eggs were candled daily to test for viability.

After incubation of the inoculated eggs the surface of the shell was sterilized by immersion in a solution of 2 per cent iodine in 70 per cent alcohol for 2 minutes, followed by 70 per cent alcohol for 2 minutes. The eggs were then drained, crushed between the halves of a sterile Petri dish, examined with sterile instruments, and the tumors in the yolk sac were measured and ground in saline solution for further passage. The average number of eggs inoculated at each passage was 10. All eggs used in this study were from a private flock of white leghorn chickens.

Observations During Serial Yolk-Sac Passage

The C3H tumor was implanted in the yolk sac on May 31, 1943, after 13 passages in mice of the parent strain or their F_1 hybrids. During the early serial yolk-sac passages of the tumor transfers were made at 12-day intervals. After 8 passages the majority of the embryos began to die before the 12th day after inoculation, and it was necessary to make transfers at shorter intervals in order to maintain the tumor. With continued passage the embryos died at shorter and shorter periods after inoculation, and on a number of occasions during the later of the 20 passages most of the embryos died the night before transfer was contemplated, leaving only 1 or 2 alive from which the tumor could be transferred. The consecutive intervals of transfer for the first 19 of the yolk-sac passages were 12, 12, 12, 12, 12, 12, 11, 12, 11, 10, 11,

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9, 9, 9, 9, 9, 8, 8, and 8 days respectively. In the 20th passage the 6 eggs that were to have been opened on the eighth day after inoculation died on the night of the seventh day, December 20, 1943, and the egg passage tumor was lost.

The tendency of the embryos to die at progressively shorter intervals is shown by the percentage surviving over an arbitrarily chosen period. The percentage of embryos surviving through the ninth day was computed for each of the first 16 egg passages. The average percentage surviving in egg passages 1 through 4, 5 through 8, 9 through 12, and 13 through 16 was 63, 56, 49, and 28 respectively. Since transfers after the 16th passage were made at intervals of 8 days the number of survivors cannot be compared with the foregoing series. The average proportion of survivors over a period of 8 days for the final 4 passages was, however, 29 per cent.

The increasing mortality rate of the embryos on continued egg passage of the tumor was not associated with an acceleration of its growth rate. During the early passages at 12-day intervals the tumors were relatively large, commonly measuring 9 to 17 mm. in diameter and weighing 1 to 3 gm. With passage at shorter intervals the tumors were correspondingly smaller. The eggs in the later passages of the series that were opened after 8 or 9 days of incubation yielded only relatively small tumor nodules, 3 to 4 mm. in diameter, around the edge of the umbilicus of the yolk sac. The increasing mortality rate of the embryos in the later passages was thus not related to the size of the tumors.

Cultures of the yolk were made in approximately half of the cases in which the embryos died spontaneously. In only 3 was there evidence of bacterial contamination, and in each case this contamination was due to micrococci. It is evident that bacterial contamination did not explain the spontaneous deaths of the inoculated embryos. The tumor material used for transfer in the series was found in every instance to be bacteriologically sterile by cultures in dextrose-brain broth and blood agar.

Repeated efforts to carry a mammary carcinoma originating in the A strain by serial yolk-sac passage were less successful than the attempts to carry the C3H tumor. The primary inoculation with mouse tumor suspension yielded relatively large growths after 12 days of incubation, but the second or third yolk-sac transfer resulted in death of the embryos after 3 to 6 days. With this tumor it appeared that the tendency to produce a lethal effect upon the embryo was attained much more rapidly on yolk-sac passage than in the case of the C3H carcinoma.

Growth of the C3H Yolk-Sac Passage Tumor in Foreign Strains of Mice

The susceptibility of inbred strains of mice was tested to grafts of two "egg" tumors that had been transplanted into mice after the fifth and the 11th serial passage in eggs. These tumors are designated as H5 and H11 respectively.

The tumors were carried in mice of the C3H strain, C3H F_1 hybrids, and C3H back-cross mice. In addition, mice of the following strains were tested: A, C57 black or B, C albino, and sublines 212 and 12 of the D or dilute brown stocks.

Both tumors grew rapidly in C3H and their hybrid animals and were transplanted every 10 to 14 days, usually by the trochar method.

The H5 tumor was inoculated into 120 C3H mice or their hybrids and 11 animals of the same groups were used to continue the H11 tumors. The tumors grew progressively in all animals. There was no apparent difference in the rate of growth of the two, although they were not transplanted simultaneously in many animals to test this fact. The majority of the mice did not have the active milk agent.

On August 18, 1943, 14 mice of the inbred A strain were inoculated subcutaneously with grafts of the C3H tumor, H5. None of the animals gave palpable nodules. These mice were reinoculated on August 30, 1943, with the same tumor and again the results were negative.

Fifty mice of the C57 black, C albino, A albino, and sublines 212 and 12 of the dilute brown stocks were inoculated with tumor H11 on November 10, 1943, and the surviving animals were reinoculated with the same tumor on December 11, 1943. In 47 (94 per cent) tumors developed, ranging from 0.5 to 5 cm. in diameter. Three of the 47 mice, all members of subline 12 of the dilute brown stock, died, presumably from their growths.[1] All the other tumors had regressed within 4 weeks. None of the mice that had tumors after the initial inoculation showed growths after reinoculation. Of the 3 mice that were negative after the initial inoculation, 2 showed small tumors after the second inoculation. These growths regressed within a few weeks.

Filtrates (Berkefeld and Seitz) of the H5 tumor were injected subcutaneously into males of the highly cancerous C3H strain. Tumors did not result. Filtrates of the H11 tumor were not tested.

Attempts to Find a Cell-Free, Tumor-Inducing Agent in Tumor-Bearing Eggs

Several attempts were made to find a cell-free, tumor-inducing agent in material from tumor-bearing

[1] Five mice of subline 12 were inoculated. Four mice of subline 212 had temporary masses after the initial inoculation.

eggs. In each instance material from eggs bearing relatively large tumors, which weighed from 1 to 3 gm., was used for study. In every case the material was taken from eggs containing living embryos, and was handled as rapidly as possible to prevent inactivation of any tumor-inducing agent that might be present. Tests for such an agent were performed by the subcutaneous injection of 0.8 cc. of the material into the mammary region of adult female mice of the parent strain or parent strain back-cross mice.

Experiments with the C3H tumor.—When the untreated yolk surrounding large tumors was injected subcutaneously into mice, tumors commonly developed in 10 to 30 days. Five different specimens of yolk were inoculated into a total of 8 mice, and tumor growth resulted in 6. Histologic sections of the tumors showed them to have a structure similar to that of the original mouse tumor. It appeared probable that there were living tumor cells in the yolk surrounding the tumors.

Several yolks, together with an equal volume of saline solution, were passed through a Berkefeld N filter and inoculated into 2 mice. No tumors appeared during 112 days of observation. Even when yolk material was diluted 4 times with saline solution the pressures necessary to force the mixture through Berkefeld N filters, as measured by a mercury manometer, were so great as to make the filtration unreliable. Because of this fact attempts to obtain a cell-free agent by filtration were not continued.

On 2 occasions 3 yolks were pooled and rapidly frozen and thawed 3 times by alternate immersion in a mixture of carbon dioxide snow and alcohol, and in water at room temperature. This material was injected at once into mice, 3 for each of the 2 specimens. After 42 days there was no evidence of tumor growth.

Another specimen containing several yolks was shaken with cold ether and quickly centrifuged. The supernatant ether was discarded and part of the remaining material was injected into 2 mice. After 62 days no evidence of tumor growth was present.

In 2 instances the blood and allantoic fluid from several embryos bearing large tumors in the yolk sacs were centrifuged at 3,000 revolutions per minute for 5 minutes in an angle centrifuge. The sediment from each specimen was injected into the mammary region of 2 mice. At the end of 33 days the 4 mice did not show any evidence of tumor growth.

Experiments with the A tumor.—Three yolks and yolk sacs were emulsified in a mortar together with 2 volumes of saline solution, filtered through paper by suction, and frozen in a mixture of carbon dioxide snow and alcohol. The thawed material was injected into 3 mice. This experiment was repeated on another occasion. After 30 days none of the 6 mice showed evidence of tumor growth.

Three different specimens, each containing several yolks and yolk sacs, were frozen and thawed rapidly 3 times and injected into a total of 8 mice. After 60 days of observation there was no evidence of tumor growth.

COMMENT

The reason for the increasingly lethal effect on the chick embryo of the implanted C3H strain tumor during serial transfer in the yolk sac is not clear. The possibility that a virus accompanied the tumor and gradually increased in virulence with passage may be considered. Taylor and his co-workers (19) have described a depression of the hemoglobin level in embryonic chicks bearing an implanted tumor in the yolk sac, the severity of the depressant action being in direct relation to the size of the growth. In the present experiments the lethal effect on the embryo was not in relation to the size of the tumor. A change of susceptibility in the embryos could explain the increasing mortality rate in the later yolk passages of the tumor, but this hypothesis is not probable, for during the entire period of transfer of the egg-passage tumor other growths were being inoculated successfully from mice into eggs and were growing to a large size.

The successful transplantation of tumors into mice is usually dependent upon the relation of the genetic constitution of the tumor grafted to that of the host inoculated (12). Each transplanted tumor, even each one of multiple spontaneous tumors from a single host (4, 5, 8, 16), has been found to have a definite genetic constitution, and only animals that have the same growth factors will respond by allowing the tumors to grow progressively.

Mammary neoplasms have been observed to "mutate" during the process of transplantation (4, 8, 14, 15), that is, they become less specific, and require a smaller number of growth factors for successful transplantation. The growth rate of the mutant tumors was usually greater than before mutation, but their histologic appearance was not necessarily changed.

It has been unusual to find tumors developing in mice of inbred strains that would grow progressively in those of unrelated homozygous strains (6), but after mutational changes Strong (15) found one that would grow in all mice and Cloudman (8-10) described 2 transplantable mammary tumors that would grow in mice other than those of the parental strain. It was not stated whether these tumors would grow in this manner when they were first transplanted or whether the specificity of the cells had changed during propagation.

Attempts to immunize mice of inbred strains against their own tumors have usually been unsuccessful (3, 7). On the other hand, it has been possible to induce immunity in mice of inbred strains to a few tumors that had developed in mice of unknown ancestry but would grow progressively in these animals (for literature see 1, 2, 3, 7). In these experiments it was determined that the genetic constitution of the inoculated host played an important role in the development of immunity. Likewise, the site of subcutaneous inoculation had to be considered. That is, if the grafts were placed in positions or sites where the blood supply was not as abundant as in others they would grow more slowly; as a result, more tumors would regress and the host would be immune against other grafts of the same or other tumors (2, 7). In one study (7) the temporary growth of the tumor was not a prerequisite for immunity.

Barrett (3) found that immunity to tumor 15091a (8-10), which developed in a mouse of the A strain, might be induced in unrelated strains by the injection of defibrinated blood from mice of other stocks, whereas homologous blood gave insignificant differences. Thus the degree of resistance depended upon the genetic relation of the host, the tumor, and the donor. Immunity could not be produced in mice of the A strain.

In the present experiment it seemed probable that the genetic constitution of a mammary carcinoma from a mouse changed during serial passage in chick embryos. Previous to the "mutation" the tumor from eggs would grow progressively when transplanted into mice of the inbred strain in which it developed, but would not give palpable nodules in mice of another inbred strain. After the change of specificity, between the sixth and 11th passage in eggs, grafts would show temporary growth in mice of several unrelated inbred strains. After spontaneous regression of their tumors the mice were resistant to further inoculation of the same growth. Mice of the strain in which the tumor developed grew the tumor progressively and few of the animals survived for longer than 3 weeks after inoculation.

The several attempts to obtain a cell-free agent, capable of inducing tumors in mice, with material from tumor-bearing eggs resulted in failure. Many of the known viruses would have withstood the freezing and thawing method used to destroy the cells in these experiments, but since the number of animals used in these attempts was small no definite conclusions can be drawn.

SUMMARY

A mammary carcinoma of the mouse has been cultivated in the yolk sac of the developing chick embryo for 20 serial transfers. With yolk-sac passage of the tumor the embryos died at progressively shorter intervals. Death of the embryos was not related to the size of the tumor.

Transplantation of the tumor into mice after serial passage in chick embryos gave data that suggested changes in the genetic constitution of its cells while they were being propagated in the eggs.

Previous to the change mice of an unrelated strain were resistant to inoculation, but after the "mutation" mice of several stocks showed temporary growth of the tumor. After regression of the transplants mice of the unrelated strains were immune to reinoculation.

Whereas none of the mice of the strain in which the tumor developed survived inoculation, only a few mice of one unrelated strain showed progressive growth of the grafts.

A limited number of attempts to find a cell-free agent in material from tumor-bearing eggs that would produce tumors in mice resulted in failure.

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Abstracts

Experimental Research, Animal Tumors

Minimal Number of Anesthetic Treatments with Urethane Required to Induce Pulmonary Tumors. HENSHAW, P. S. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:523-525. 1944.

Strain A mice were given anesthetizing doses of urethane by intraperitoneal injection once a week for from 1 to 5 weeks, beginning when they were 6 to 8 weeks old. They were killed when 6 months old. Numerous lung tumors were found, even in the animals that had received only a single dose. Control strain A mice rarely develop lung tumors when less than a year old, although the incidence amounts to 75% at 18 months. Tumors of organs other than the lungs were not found.—H. Q. W.

The Chemistry of Cerebral Tumours and of Cerebral Cyst Fluids. CUMINGS, J. N. [National Hosp., London, England, and a Neuro-Surgical Unit, E. M. S., Section 9] *Brain*, **66**:316-321. 1943.

The water, potassium, sodium, chloride, and phosphorus content were determined in 47 cerebral, and 5 spinal tumors. Thirty-eight cerebral tumors and 26 cerebral cysts were examined to determine the amounts of nucleoprotein, phospholipid, and acid soluble phosphorus present. No consistent difference in water content between various tumors was found. Those showing a phosphate content above the average were usually necrotic tumors. A raised level of calcium may be found in any tumor. The amount of nucleoprotein was small as was the phospholipid content. The author suggests that the majority of cysts were formed by degeneration of tumor tissue since the former had a moderate amount of nucleoprotein.—E. E. S.

Metabolic Studies in Patients with Gastro-Intestinal Cancer. IV. Fat Metabolism, A Method of Study. REKERS, P. E., ABELS, J. C., and RHOADS, C. P. [Memorial Hosp., New York, N. Y.] *J. Clin. Investigation*, **22**:243-248. 1943.

The gasometric method of Van Slyke *et al.* was adapted to measure the absorption of fat from the gastrointestinal tract of a group of subjects. The group included 2 normal persons, 1 patient bearing gastric carcinoma, 1 who had undergone total gastrectomy, 1 with generalized atrophic gastritis, and 2 patients with hepatic cirrhosis. An abnormal absorption of fat was demonstrated only in the gastrectomized patient and in the patient with atrophic gastritis. The question is raised of a possible relationship between the absence of an intact gastric mucosa and the normal absorption of fat from the gastrointestinal tract.—J. L. M.

Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. V. Pancreatic Insufficiency in a Patient Treated Surgically for Carcinoma of the Ampulla of Vater. REKERS, P. E., PACK, G. T,. and RHOADS, C. P. [Memorial Hosp., New York, N. Y.] *J. A. M. A.*, **122**:1243-1245. 1943.

The patient, who had had the duodenum and the head of the pancreas resected and the pancreatic ducts ligated, presented the clinical picture of pancreatic insufficiency. Clinical improvement followed the administration of large quantities of pancreatic enzymes. A decrease in the amounts of fat and nitrogen excreted in the feces was noted. An increase in the protein content of the diet resulted in increased absorption of fat. An increase in the dietary fat resulted in increased fat absorption but no reduction in amount of fat lost.—M. E. H.

Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. ARIEL, I. M., ABELS, J. C., MURPHY, H. T., PACK, G. T., and RHOADS, C. P. [Memorial Hosp., New York, N. Y.] *Ann. Int. Med.*, **20**:570-579. 1944.

Observations were made on a test group of 18 patients with gastrointestinal cancer, and on 2 control groups with 4 patients in each, the preoperative preparation in all cases being the same. A small specimen of the liver (0.8 to 1.5 gm.) was removed at operation and analyzed chemically for glycogen and for total lipid; a part of it was also studied histologically. Values for total protein, and for "albumin" and "globulin" in the liver were also obtained in 12 of the cases, and in these the serum protein levels were also studied.

The recorded figures indicate that there was frequently more fat in the liver, as determined chemically, in patients with gastrointestinal cancer than was the case in the control patients in which there was no hepatic involvement; yet the histological analyses revealed that only 2 of the liver specimens from patients of the test group showed moderate fatty infiltration, the rest appearing normal although some contained even larger amounts of total fat, as determined chemically, than the 2 specimens with visible fatty infiltration. The figures for liver glycogen were about the same in the patients of the test and control groups, but the authors consider that there was probably glycogen depletion in the cases of gastrointestinal cancer. No relationship could be found between the concentration of protein in the serum and in the liver of patients with gastrointestinal cancer.—J. G. K.

Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract. IX. Effects of Dietary Constituents upon the Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. Abels, J. C., Ariel, I. M., Murphy, H. T., Pack, G. T., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *Ann. Int. Med.*, **20**:580-589. 1944.

Glucose, lipocaic, choline chloride, or inositol were administered preoperatively to 37 patients with gastrointestinal cancer, and to 12 patients with benign gastrointestinal lesions. At operation, specimens of the livers were procured and analyzed chemically for glycogen and for total lipid; total protein was also determined in some instances.

The findings are recorded in 9 tables, each of which contains data on from 2 to 11 patients; for comparison the results in 26 patients untreated preoperatively are likewise tabulated. The recorded figures indicate that the preoperative oral administration of glucose to patients with gastrointestinal cancer, common bile duct obstruction, or benign gastrointestinal lesions significantly decreased the concentration of fat in their livers, without affecting notably the concentration of hepatic protein. Patients with gastrointestinal cancer who had received lipocaic before operation likewise had less fat in their livers than was present in the specimens from other patients with gastrointestinal growths who had not been treated preoperatively. Patients given inositol preoperatively had livers containing comparatively little fat, as determined chemically, while others given choline provided specimens with rather more fat in general than was present in the specimens from the other treated patients, though rather less than the quantity found in the livers of untreated cases.

None of the substances administered preoperatively seemed to influence the total protein level of the livers, and lipocaic did not seem to affect significantly the concentration of liver glycogen. The administration of glucose increased the hepatic glycogen stores significantly only in patients with benign gastrointestinal disorders.—J. G. K.

Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. X. Hypoproteinemia and Anemia in Patients with Gastric Cancer. Ariel, I., Rekers, P. E., Pack, G. T., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *Ann. Surg.*, **118**:366-371. 1943.

Ninety-seven patients with gastric carcinoma were studied. It was found that in 59% the concentration of serum protein was below 6.6 gm. per cent and that 70% of patients were anemic. The hypoproteinemia was due to deficiency of serum albumin alone in 73% of those with low serum protein. A comparison of the data for normal individuals and for patients with gastric carcinoma, benign gastric lesions, and oral leukoplakia showed no correlation of hypoproteinemia or anemia with economic status, age, or diet. Bleeding from the gastrointestinal tract had no significant influence on the percentage of hypoproteinemia and anemia in gastric cancer, and 10 patients with cancer of the stomach excreted normal amounts of nitrogen in the stools. Among 12 patients on whom resection of a gastric neoplasm had been performed, none had hypoproteinemia, and 25% were anemic.—W. J. B.

Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. XII. The Glycine Tolerance Test in Patients with Gastric Cancer. Ariel, I., Jones, F., Pack, G. T., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *Ann. Surg.*, **117**:740-747. 1943.

Because of the high percentage of patients who develop hypoproteinemia with gastric cancer, the authors have studied the absorption of amino acids from the gastrointestinal tract by means of the glycine tolerance test. In 5 patients with adenocarcinoma of the stomach and 1 with squamous cell cancer of the terminal esophagus, the peak of amino-acid-nitrogen levels occurred during the second hour and 5 of the peaks were higher than the greatest value in the control group. This peak occurred during the first hour in 5 of 6 patients with neoplastic disease of the extremities and in 2 of 3 patients with benign lesions of the stomach. In 1 case of the latter group a peak of absorption occurred during the first hour with a secondary higher rise during the third hour. After gastric resection in the 3 cases of gastric and esophageal neoplasms and Boeck's sarcoid respectively, the peak of glycine absorption was reached in the first hour. It is felt that altered motility, or some metabolic disturbance, or both, resulting in delayed absorption of amino acid, contributes to the high incidence of hypoproteinemia in cases of gastric cancer.—W. J. B. (*See* abstracts *Cancer Research*, **4**:201; 262. 1944.)

The Oxidative Response of Normal and Neoplastic Tissues to Succinate and to *p*-Phenylenediamine. Rosenthal, O., and Drabkin, D. L. [Univ. of Pennsylvania, Med. Sch., Philadelphia, Pa.] *Cancer Research*, **4**:487-494. 1944.

The absolute oxidative response to the addition of *M*/20 succinate or *p*-phenylenediamine was studied in normal tissues of rabbit, rat, and man, and in neoplasms of the latter two species.

Thin slices or fine minces of fresh tissues were examined by means of the Warburg technic. A criterion, *the critical rate of oxygen consumption*, was introduced to serve in the objective evaluation of "maximal" oxygen consumption rates that can be measured with the types of preparations employed. The manometric studies were accompanied by histological examination of the material. To correct for the variable factors of inert tissue mass and storage substance, the protein-bound phosphorus content of the tissues was used as a standard of reference for the quantitative data.

The following results were obtained:

1. Normal epithelial tissues fall into two main groups: (a) tissues with high oxidative responses towards succinate or *p*-phenylenediamine (kidney cortex, liver, brain cortex, and probably smooth and striated muscle); (b) tissues with low responses toward the 2 test substrates (gastrointestinal mucosa, lung, and possibly skin, mammary gland, and lymphatic tissue). The position of the submaxillary gland is intermediate between the two main groups.

2. Benign and malignant rat tumors as well as human cancers show remarkably uniform oxidative responses of a low order of magnitude, similar to that found in normal group (b).

It follows that changes of the oxidative behavior incident to a malignant transformation can be expected to

occur only in types of tissue belonging to normal group (a). Within this group, the divergence of the oxidative behavior from that of the parent tissue should serve as an objective criterion of the degree of dedifferentiation of neoplasms. With the method of evaluation here suggested the examination of the response to succinate alone would fulfill this purpose. It is pointed out that the method of Craig, Bassett, and Salter, who utilize the percentile oxidative responses to succinate ($M/50$) or *p*-phenylenediamine ($M/100$) in a glucose medium as a standard of comparison, cannot be considered a reliable index of the activities of the succinic dehydrogenase or of the cytochrome system.—Authors' abstract.

The Non-Heme Iron Content of the Tissues of Mice of High-Cancer and of Low-Cancer Strains. Warren, F. L., and Goulden, F. [Royal Cancer Hosp., (Free), London, England] *Cancer Research*, **4**:417-420. 1944.

In some species the aging of an animal is accompanied by a definite increase in the non-heme iron content of the tissues. Estimations of non-heme iron in the kidneys of mice of 2 high-mammary-cancer strains (RIII and C3H) and 1 low-mammary-cancer strain (CBA) were made with a view to detecting differences in physiological age between high- and low-mammary-cancer mice at the same chronological ages. No such differences were found. Female mice of the CBA strain showed a considerable increase in kidney non-heme iron between 300 and 400 days of age. With this exception no great difference was found between young and old mice of either sex in any of the mice investigated.

The great increase in the non-heme iron content of the tissues of old rats was confirmed for both sexes. The non-heme iron content of the kidneys of old female rats was higher than that of the kidneys of old male rats to a highly significant extent.—Authors' summary.

The Hemoglobin Content of the Blood of Mice of the RIII and CBA Strains. Goulden, F., and Warren, F. L. [Royal Cancer Hosp. (Free), London, England] *Cancer Research*, **4**:421-424. 1944.

Blood hemoglobin was estimated in both sexes of 2 strains of mice. In both strains (CBA low-mammary-cancer; RIII high-mammary-cancer) the concentration of blood pigment was higher in female mice than in male mice at all ages. Female mice of the RIII strain showed a rapid fall of blood hemoglobin between the ages of 360 and 430 days. This fall amounted to about 10% of the blood pigment initially present and occurred at the age at which spontaneous mammary carcinoma normally begins to appear in female mice of this strain.—Authors' summary.

Genetic Analysis of the Induction of Tumors by Methylcholanthrene. VII. Primary Carcinoma of the Liver Following Subcutaneous Injection of Methylcholanthrene in Mice. Strong, L. C. [Yale Univ. Sch. of Med., New Haven, Conn.] *Arch. Path.*, **37**:131-135. 1944.

Nineteen cases of primary carcinoma of the liver were encountered in 17 of approximately 2,000 NHO mice that had been given a subcutaneous injection of 1 mgm. of methylcholanthrene dissolved in 0.1 cc. of sesame oil at the age of 2 months. The animals had been selected on a genetic basis as being resistant to the induction of tumor at the site of injection. No hepatic tumors were found in 2,000 unselected NH mice treated in the same way with methylcholanthrene. The author concludes that hybrid mice, such as those of the NHO descent, are endowed with the capacity to give rise to a great number of tumors of various parts of the body following the subcutaneous injection of methylcholanthrene, but that these tendencies can be detected only when the development of tumors of such types as fibrosarcoma, rhabdomyosarcoma, and epidermoid carcinoma at the sites of injection are eliminated or suppressed by genetic selection.—J. G. K.

Mammary and Testicular Tumours in Male Mice of Various Strains Following Œstrogen Treatment. Bonser, G. M. [Univ. of Leeds, Leeds, England] *J. Path. & Bact.*, **56**:15-26. 1944.

Triphenylethylene (3 mgm. in sesame oil *sub cutem* weekly) were given from the age of 4 to 5 weeks until death. The results were as follows:

Incidence of testicular tumors.—(1) Normal "white label" (Kreyberg) and IFS mice. An increase in the size and number of interstitial cells, and late in the experiment (60th to 100th week) a small number of non-metastasizing interstitial-cell adenomas and carcinomas. (2) RIII males. Atrophy of the testes and a high rate of mammary cancer (15 cancers in 24 mice). (3) RIII males fostered by CBA females. Great reduction of mammary cancers allows longer survival. Of 38 mice living for 50 weeks or more, 14 showed unilateral or bilateral testicular adenomas or carcinomas. (4) RIII males fostered by Strong A females. One-half of the mice developed mammary cancer; 7 bore unilateral or bilateral testicular adenomas or carcinomas. The numbers available do not allow a comparison of the effect of foster nursing by Strong A, or by CBA females, on the appearances of testicular tumors. (5) CBA mice fostered by RIII females. A high incidence of mammary cancer; often some hyperplasia of interstitial cells but no tumors. (6) Strong A mice, whether suckled normally or by RIII females, showed a high incidence of malignant interstitial-cell tumors (*e.g.* 8 in 9 mice).

Incidence of mammary cancer.—(1) "white label," 45%. (2) IFS, nil, but when fostered by RIII, tumors occurred in breeding females and estrogen-treated males. (3) RIII. Fostering by CBA reduced the incidence in estrogen-treated males from 62.5% to 4.3%. The incidence after fostering by Strong A was lower and later than in normal RIII (? difference in milk factor). (4) CBA. Fostering by RIII raised the incidence in males from 0 to 77%. (5) In contrast to (4), Strong A females fostered by RIII gave no tumors. (6) Triphenylethylene caused a somewhat higher incidence in castrated than in normal Strong A males.

"Pelvic organs."—A comparison of the "pelvic organs" in the various classes of mice showed less keratinization where interstitial-cell hyperplasia or tumors developed, the differences being due presumably to androgen secreted by this tissue.

The histology of the tumors and of the adjacent lymph nodes is described and illustrated by 14 photomicrographs.

An interstitial-cell carcinoma in a Strong A male was successfully grafted into a normal female and into estrogen-

treated males. In subsequent generations it was grafted from the normal female into normal females and males. This work and that of others shows that the strains Strong A, RIII, JK, and C are especially susceptible to the production of interstitial-cell testicular tumors by estrogens. The milk factor seems not to affect the incidence of these tumors except indirectly through the effect of mammary carcinoma on longevity. Estrogen treatment of males of IFS and "white label" strains causes mammary cancers to appear in the same proportion as in untreated females, but in similarly treated Strong A males, whether normal or fostered by RIII, the number of mammary cancers remains very low, although the incidence in breeding Strong A females is 50%. Castration had little effect in raising the incidence of mammary cancer in estrogen-treated Strong A males, hence in this strain there appears to be some other factor as yet unknown.—E. L. K.

Antifibromatogenic Effects Produced by the Intermittent Action of Progesterone. Iglesias, R., Lipschütz, A., Nieto, G. [National Health Service of Republic of Chile, Santiago, Chile] *Cancer Research,* **4**:510-511. 1944.

Uterine and other abdominal fibroids induced in the female guinea pig by the prolonged action of subcutaneously implanted tablets of estradiol can be prevented by progesterone, even when the antifibromatogenic steroid is allowed to act only intermittently.

These findings support the concept that the rhythmic secretion of progesterone in the ovary is a means of bodily autodefense against the toxic and tumor-producing reactions of estrogens.—Authors' summary.

Inactivation of Antifibromatogenic Substances (Progesterone and Desoxycorticosterone Acetate) in the Liver. Dosne, C. [National Health Service of Republic of Chile, Santiago, Chile] *Cancer Research,* **4**:512-514. 1944.

Progesterone and desoxycorticosterone acetate (DCA) are antifibromatogenic substances in that they neutralize the fibromatogenic effects of estrogens. Progesterone and DCA tablets were introduced into the spleen, that is, made to drain directly into the portal circulation. Using the fibrous tumorous effect (F.T.E.) as an index, it was found that these substances were inactivated by the liver. Observations also showed, however, that above a certain dose a portion of the hormone escapes inactivation.—Author's abstract.

Experimental Modification of Radiosensitivity of Embryonal Cells. Goodrich, J. P. [State Univ. of Iowa, Iowa City, Iowa) *Radiology,* **40**:179-187. 1943.

Grasshopper eggs were irradiated at various developmental stages at temperatures of from 1 to 3° C. and after dehydration. Low temperatures decreased sensitivity before the third day of pre-diapause development and increased sensitivity after the third day of pre-diapause and the first 2 days of post-diapause. Dehydration caused an increase in sensitivity before the fifth day of pre-diapause development and a decrease in sensitivity during the remainder of pre-diapause and on the second day of post-diapause. Apparently low temperature modifies the oxidative mechanisms, and dehydration alters the osmotic relations of the cells to the fluids bathing them. Radiosensitivity may be modified in opposite directions by the same modifying agent at different stages of development.—R. E. S.

Experimental Roentgen Injury. I. Effects on the Tissues and Blood of C3H Mice Produced with Single Small Whole-Body Exposures. Henshaw, P. S. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.,* **4**:477-484. 1944.

A study was made of the effects of small doses of roentgen radiation applied to the whole bodies of C3H mice. The radiation factors were: 200 kv., 20 ma., 0.5 mm. Cu + 1.06 mm. Al filter, 105 cm. distance, 8.0 r/min. intensity; 50 r total dose. Thirty-nine animals were used. Blood counts were made, and tissues were obtained at intervals of from 1 hour to 14 days after irradiation.

A transitory leukocytosis was present from 2 to 4 hours after irradiation. This was followed by a slight leukopenia, which persisted for at least 2 weeks. In the lymph nodes and spleen debris appeared in 2 to 4 hours; this soon disappeared, and at 8 to 12 hours a mild hyperplasia developed. Changes in bone marrow were slight but suggested that some immature cells had been destroyed. The seminiferous tubules of the testis showed a significant reduction of spermatogonia and primary spermatocytes at 1 week, and of secondary spermatocytes at 2 weeks. Regeneration took place, and the tubules appeared normal again in 4 to 6 weeks.—H. Q. W.

Experimental Roentgen Injury. II. Changes Produced with Intermediate Doses and a Comparison of the Relative Susceptibility of Different Kinds of Animals. Henshaw, P. S. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.,* **4**:485-501. 1944.

A study was made of the effect of roentgen ray doses of 50, 100, 200, and 400 r delivered to the whole bodies of C3H and LAF_1 mice and pure bred National Institute of Health guinea pigs. Roentgen factors were the same as those employed in the previous study (*J. Nat. Cancer Inst.,* 4:477. 1944) except that distances were decreased and the guinea pigs were cross-fired from 2 beams. Thus intensities of 38 r/min. were used for the mice and 71 r/min. for the guinea pigs.

It was found that the three types of animals differed considerably in radiosensitivity, the approximate lethal doses being—guinea pigs, 200 r; C3H mice, 450 r; LAF_1 mice, about 600 r. The changes seen in leukocyte count and in the microscopic appearance of lymphoid tissue, spleen, bone marrow, and testis were of the same type as those found in the previous study, except that, with the higher doses, the changes were more pronounced and recovery was slower. It appeared that, in all the tissues, the intermediate type cells were destroyed. Later regeneration in each series started from the stem forms, which appeared more radioresistant than the intermediate forms.—H. Q. W.

Experimental Roentgen Injury. III. Tissue and Cellular Changes Brought About with Single Massive Doses of Radiation. Henshaw, P. S. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.,* **4**:503-512. 1944.

Massive doses of roentgen rays were delivered to the whole bodies of C3H mice, guinea pigs, and rabbits. The

factors were: 200 kv., 20 ma., no filter, 50 cm. distance, 250 r/min. intensity, 25,000 to 50,000 r total dose.

The animals differed somewhat in response to treatment, but usually developed fever, tachycardia, cyanosis, and spasticity as soon as the dose had reached 25,000 r. Death occurred at various intervals up to 48 hours. Profound leukopenia developed immediately after treatment. No immediate change took place in erythrocyte count, but, in animals surviving as long as 24 hours, there was a rise suggesting hemoconcentration. Microscopic examination showed that all tissues in the body were profoundly damaged. Lymphoid tissue and bone marrow were almost completely necrotic, only a few primitive type cells appearing viable.—H. Q. W.

Experimental Roentgen Injury. IV. Effects of Repeated Small Doses of X-Rays on Blood Picture, Tissue Morphology, and Life Span in Mice. Henshaw, P. S. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:513-522. 1944.

C3H male mice were given doses of 5, 10, 15, 20, or 25 r five days per week from the age of 2 or 3 months until death. Radiation factors were: 200 kv., 20 ma., 0.5 mm. Cu + 1.06 mm. Al filter, 105.3 cm. distance, 8.0 r/min. intensity.

The total leukocyte count dropped progressively, the decrease being more noticeable in the lymphocytes, and greater with the larger doses. Terminally there was a tendency toward alternating leukocytosis and leukopenia. At autopsy, damage to the lymph nodes, spleen, bone marrow, and testis was found. Survival time varied inversely with the daily dose, but, although the animals receiving the smaller daily doses lived longer, they received less total dose before death.—H. Q. W.

Fluorescence Studies on Cancer. I. Porphyrin Metabolism, Harderian Gland Fluorescence, and Susceptibility to Carcinogenic Agents. Figge, F. H. J. [Univ. of Maryland Sch. of Med., Baltimore, Md.] *Cancer Research*, **4**:465-471. 1944.

The examination of numerous birds, reptiles, and mammals showed that red-fluorescent harderian glands were present only in mice, rats, and hamsters. The data in the literature indicated that of all the animals that have been tested, these three species are the most susceptible to induction of tumors by carcinogenic agents. Since the red-fluorescent porphyrin-excreting harderian gland reflects the porphyrin metabolism of other organs and tissues, a relationship between excess porphyrins (or a unique porphyrin metabolism) and susceptibility to carcinogenic agents is postulated. Protoporphyrin 9 and coproporphyrin I are the specific porphyrins excreted by the harderian glands.

When porphyrins were injected into the peritoneal cavity of rats, these substances soon became concentrated in the skin and subcutaneous tissues and the harderian glands. A study of the ultimate fate of the porphyrins excreted by the harderian glands showed that they are smeared on the areas of the skin of mice and rats where tumors develop when these animals are irradiated with ultraviolet light. Here, too, the only animals that have been found to be susceptible to the induction of tumors by ultraviolet light are the mice and rats, which have red-fluorescent (porphyrin-excreting) harderian glands. These data support the original hypothesis that there is a direct or an indirect relationship between porphyrins or porphyrin metabolism and cancer susceptibility.—Author's abstract.

Fluorescence Studies on Cancer. II. The Red Fluorescence of the Genitalia of Women. Jones, E. G., Figge, F. H. J., and Hundley, J. M., Jr. [Univ. of Maryland Sch. of Med., Baltimore, Md.] *Cancer Research*, **4**:472-482. 1944.

The genitalia of 121 women were examined for fluorescence in near ultraviolet light. The clitoris was red-fluorescent in 40 cases, the labia minora and majora in 16 and 13 cases respectively. Red-fluorescent secretion or exudates were observed in the vagina in 12 and on the cervix of the uterus in 11 women. When red-fluorescent material was observed on the vulva, it was always most concentrated on and near the clitoris. Red-fluorescent material was also found in the region of the corona of the glans penis in uncircumcised males. The genitalia of some women are intermittently red-fluorescent. Red fluorescence was observed most often during the menstrual or postmenstrual phase of the cycle. Putrid lochia is intensely red-fluorescent, and the fluorescent material may persist for a month or two. The occurrence of red fluorescence was not definitely related to any organic disease.

An attempt was made to discover the source of the red-fluorescent material. Most of this was thought to arise from the bacterial or histolytic decomposition of blood which exudes from the uterus. Some evidence points to a direct bacterial or glandular (cervical or sebaceous glands) origin of the red-fluorescent material. The possibility of a relationship between cancer incidence and the occurrence of red-fluorescent secretions or exudates was discussed.

While the observations lend support to the hypothesis that the red-fluorescent material is one of the causative factors in the development of malignancy, no proof of this was obtained. The significance of these observations and direct proof or disproof of such an etiological relationship is left for future investigation.—Authors' abstract.

Fluorescence Studies on Cancer. III. The Extraction and Identification of Porphyrins from the Red-Fluorescent Exudates on the Genitalia of Women. Figge, F. H. J., Jones, E. G., and Wolfe, G. F. *Cancer Research*, **4**:483-486. 1944.

The red-fluorescent material observed on the genitalia of women was collected, extracted, and identified. The data on the solubility and spectral absorption showed conclusively that the red fluorescence was related to the presence of porphyrins. Most of the porphyrin removed from the cervix was a mixture of mesoporphyrin, deuteroporphyrin 9, and coproporphyrin (probably type III); only 5% of this was protoporphyrin 9. Most of the porphyrin in the lochia was found to be coproporphyrin (probably type III). Only a relatively small amount of mesoporphyrin and deuteroporphyrin was present in lochia, about half of the porphyrin in lochia was protoporphyrin 9.

The definite spectroscopic identification of protoporphyrin and other porphyrins in the exudates removed from the region of the cervix of the uterus of women lends support to the hypothesis that porphyrins may sensitize cells to carcinogenic stimuli.—Authors' abstract.

Retarding Effect of Glyceraldehyde on Benzpyrene Sarcoma Formation in Mice. Riley, J. F., and Pettigrew, F. [Univ. of Edinburgh, Edinburgh, Scotland] *Cancer Research,* **4**:502-504. 1944.

Under the conditions of the experiment, 0.5 cc. *M*/10 glyceraldehyde injected subcutaneously into mice twice weekly for the 16 weeks during which tumors from a previous injection of 0.7 mgm. benzpyrene were to be expected, resulted in a delay in the appearance of tumors and a slight reduction in the tumor yield. This effect was essentially similar whether "fresh" (dimeric) or "old" (monomeric) glyceraldehyde was used and resembles the inhibition, previously recorded in a comparable experiment, in which propionaldehyde was employed. It remains to be determined whether differences of this magnitude are significant.—Authors' summary.

The Action of Heptanal Sodium Bisulfite Methylsalicylate and of 2,4,6-Trimethylpyridine on Tissue Cultures of Human and Mouse Carcinoma and Rat Lymphosarcoma. Cameron, G., Kensler, C. J., and Chambers, R. [Washington Square Coll., New York Univ., New York, N. Y.] *Cancer Research,* **4**:495-501. 1944.

Tissue cultures of human mammary carcinomas, rat lymphosarcoma, and their normal prototypes were exposed to various concentrations of heptanal sodium bisulfite methylsalicylate and 2,4,6-trimethylpyridine. Heptanal in a concentration of 0.002 *M* destroyed the malignant epithelium of the human carcinoma, while its normal tissue prototype and the fibrocytes and wandering cells in all the cultures were unaffected by a concentration of 0.007 *M*. Mouse mammary carcinoma epithelium showed a similar but somewhat less specific reaction. The action of heptanal on rat lymphosarcoma was highly selective and gave a differential between normal and malignant cells that was even greater than in the case of human mammary carcinomas. Trimethylpyridine exerted a similar, but less pronounced effect on cultures of human and mouse mammary carcinomas.—Authors' abstract.

The Cultivation of Malignant Cells in the Yolk Sac of the Embryonated Egg. Heilman, F. R. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet. Mayo Clin.,* **18**:223-225. 1943.

Five highly malignant tumors that had been carried by transplantation for 6 months or more, each in a different strain of mice, were used for the inoculation experiments. Two of the tumors were lymphosarcomas, 1 was a lymphoma, and 2 were mammary carcinomas. Thus far one of the tumors has been successfully cultivated in the yolk sac of the chick embryo. This tumor is a highly undifferentiated mammary carcinoma originating in C3H strain mice and carried in C3H F_1 hybrids. Emulsions of tumor from the yolk sac grew readily when implanted into the strain of mice from which the tumor originated. The tumor has been successfully transferred from yolk sac to yolk sac.—J. L. M.

Note on the Size of the Shope Rabbit Papilloma Virus. Markham, R., Smith, K. M., and Lea, D. [Molteno Inst. and Strangeways Lab., Cambridge, England] *Parasitology,* **35**:178-179. 1944.

Data on the diffusion, sedimentation, density, viscosity and electron micrography of the Shope rabbit papilloma virus, given by Sharp, Taylor, Beard, and Beard (*Proc. Soc. Exper. Biol. & Med.,* **50**:205. 1942) and by Neurath, Cooper, Sharp, Taylor, Beard, and Beard (*J. Biol. Chem.,* **140**:293. 1941) are treated according to the appropriate formulas of Markham, Smith, and Lea (*Parasitology,* **34**: 315. 1942) to give conclusions as to the size, shape, and degree of hydration of the agent, which are summarized as follows:

The virus is spherical or nearly spherical. Unhydrated it has a diameter of 48 mμ and molecular weight of 47 million. In solution it hydrates to the extent of 1.8 gm. water per gm. of unhydrated virus, causing its diameter to increase to 73 mμ, its molecular weight to 136 million, and its partial specific volume to 0.916.—A. H.

An Experimental Study of the Lateral Spread of Epidermoid (Squamous Cell) Carcinoma in Man, and the Reaction of Such a Lesion to the Wound-Healing Stimulus. Brunschwig, A., and Thornton, T. F., Jr. [Univ. of Chicago, Chicago, Ill.] *Cancer Research,* **4**:515-518. 1944.

Bisection of a squamous cell carcinoma on the back of a hand in a human patient with production of a cutaneous defect adjacent to the portion of the tumor remaining *in situ* revealed: (1) lack of stimulation of the carcinoma along the incised margin; (2) healing of the cutaneous defect from the normal skin borders, with no evidence of retention of purposeful (healing) proliferation in the malignant epithelium; (3) lateral spread of the carcinoma continued at the margins of the growth that were undisturbed by operative trauma.—Authors' abstract.

Neurilemomas in a Family of Brook Trout. Young, G. A., Jr., and Olafson, P. [Dept. Path. and Bact., New York State Veterinary Coll., Ithaca, N. Y.] *Am. J. Path.,* **20**:413-420. 1944.

All of 25 brook trout (*Salvelinus fontinalis*), most of which came from a single hatchery, had neurilemmomas that involved primarily the autonomic nervous system. Only 1 of 16 fish of 3 other species was similarly affected. Seven figures illustrate the changes, which were principally microscopical.—J. G. K.

Adenoma of the Bovine Bladder. Langham, R. F., Thorp, F., Jr., and Hallman, E. T. [Mich. Agricultural Exper. Sta., East Lansing, Mich.] *Am. J. Path.,* **20**:421-427. 1944.

In studies of bovine pyelonephritis, abnormal growths were found in the bladder in 2 cases. The neoplastic tissue was composed of mucin-producing, columnar epithelium, which did not infiltrate.—J. G. K.

Multiple Primary Tumors in Dogs. Mulligan, R. M. [Univ. of Colorado, Sch. of Med., Denver, Colo.] *Cancer Research,* **4**:505-509. 1944.

A review of the literature revealed 46 cases of multiple canine neoplasms. The ages were known in 36 dogs: 2 were less than 6 years old, 4 were 6 to 9 years, 29 were 10 to 20 years, and 1 was more than 20 years old. Of 43 animals in which sex was mentioned, 23 were females and 20 were males. In 37 dogs the breed was known: 8 were pinschers of various types; 7 were fox terriers; 5 were dachshunds; setters, St. Bernards, poodles, sheep hounds, and shepherds accounted for 2 each; and pointers, Dobermans, boxers, bulldogs, hunting dogs, spaniels, and terriers were represented by 1 each. The 123 tumors found in the 46 cases included 58 malignant and 65

benign neoplasms, among which were 36 carcinomas, 21 sarcomas, 14 adenomas, 11 leiomyomas, 9 fibromas, 9 lipomas, 5 hemangiomas, 4 mixed tumors, 4 cysts, 3 papillomas, 3 cystadenomas, and 1 each of mesothelioma, fibrolipoma, epulis, and melanoma. The main primary sites of the neoplasms included the mammae, subcutaneous tissue, skin, liver, circumanal glands, testes, thyroid, stomach, vagina, lungs, prostate, spleen, bone, buccal cavity, omentum, uterus, ovaries, small intestine, urinary bladder, and gall bladder. The combinations of malignant and benign neoplasms encountered in the 46 cases were tabulated.—Author's abstract.

Parental Influence on the Incidence of Cancer. Little, C. C. [Roscoe B. Jackson Memorial Lab., Bar Harbor, Me.] *J. A. M. A.*, **125**:93-97. 1944.

The author divides his discussion of the process of parental influence in relation to incidence of cancer into three main sections. In the first, the different mechanisms (chromosomes, cytoplasm of germ cells, nursing, etc.) by which parents may influence the development of their progeny are discussed. The nature of cancer and the various levels or periods in the life of the individual at which the incidence of cancer may be affected or influenced forms the second part of the discussion. Lastly, the experimental evidence derived from animal studies in the specific fields of cancer research is briefly reviewed.—M. E. H.

The Biography of Cancer. Podolsky, E. [Brooklyn, N. Y.] *M. Rec.*, **156**:290-293. 1943.

The author presents a brief review of some aspects of cancer research in the past and various theories of the cause of cancer.—E. E. S.

Clinical and Pathological Reports

Cancer and Marital Status. Dorn, H. *Human Biol.*, **15**:73-79. 1943.

Analyses of various statistics have indicated that death rates for married and single women are affected by social status, but within each social class, cancer of the breast causes more fatalities among single women, while the death rate from uterine cancer is higher among married women. The total mortality from the two combined is not determined by marital state. Australian statistics gathered between 1919-1923 reveal the highest death rate from cancer for both sexes to be among married persons without children. With the exception of breast and uterine cancer the mortality rate for tumors of various sites varies little with marital status.—E. E. S.

Diagnosis—General

The Robertson Test for Carcinoma. A Preliminary Report. Hardesty, W. L., and Love, B. [McMillan Hosp., Charleston, W. Va.] *West Virginia M. J.*, **39**:151-153. 1943.

The technic of demonstrating the clotting of a patient's blood in his own urine (Robertson test for carcinoma) is described. A report is given of tests made on 46 patients in whom the diagnosis of malignant tumor was either established or ruled out. A positive test of clot formation was obtained in 12 instances, 11 of which were associated with malignant tumors. Eight studies gave doubtful results; 4 of these were on patients with tumor. Twenty-six tests were negative, although 8 of these were on patients with malignant tumors.—E. E. S.

Therapy—General

Cancer: Results of Treatment. Nathanson, I. T. [Harvard Med. School, Massachusetts General Hosp. and Pondville Hosp.] *New England J. Med.*, **229**:468-480. 1943.

A review article published also in the Medical Progress Annual series. A chart shows the curability rate for various types of cancer. There is a bibliography of more than 200 titles.—C. W.

Coley's Mixed Toxines of Erysipelas and Prodigiosus. Report of Two Cases of Inoperable Sarcoma Treated by Coley's Method. Lilienthal, H. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **10**:623-626. 1944.

The author reports 2 cases of inoperable sarcoma treated by Coley's method. One patient remained well for about 9 years, dying of a disease not associated with new growth. The second patient is well 19 years after treatment. The author states that the toxines have the advantage of acting in generalized tumors when there are distant metastases that could not be reached by x-ray or radium.—A. Cnl.

Skin and Subcutaneous Tissue

Treatment of Birthmarks. Bailey, W., and Kiskadden, W. [Los Angeles, Calif.] *Cal. and West. Med.*, **59**:265-268. 1943.

A general discussion.—W. A. B.

Neurotic Excoriations and Epithelioma. Haber, H. [London, England] *Proc. Roy. Soc. Med.*, **37**:290. 1944.

The patient, a girl aged 20, developed a slight acne eruption on the face 4 years ago. She "could not help picking the lesions and some secondary infection and scarring developed on the nose." During treatment with lotions and sedatives, "she developed within 6 weeks an epithelioma about the size of a silver threepence on the right temple." There was no evidence of a preexisting mole. In the discussion Dr. J. H. Sequeira recalled similar cases at the ages of 11 and 18.—E. L. K.

Familial Tuberous Sclerosis (Epiloia) without Adenoma Sebaceum. Report of Two Cases. Lichstein, J., and Solis-Cohen, L. [Jewish Hosp., Philadelphia, Pa.] *J. A. M. A.*, **122**:429-432. 1943.

The more frequent use of roentgenography and pneumoencephalography is recommended in cases of epilepsy to establish the diagnosis of this neurocutaneous syndrome, even in the absence of adenoma sebaceum.—M. E. H.

Pathogenesis and Experimental Therapy of Keloids and Similar Neoplasms in Relation to Tissue Fluid Disturbances. Marshall, W., and Rosenthal, S. [City Hosp., Mobile, Ala.; and Milwaukee, Wis.] *Am. J. Surg.*, **62**:348-357. 1943.

A general discussion.—W. A. B.

Massive Fibroma of the Scalp. Case Report. McConnell, L. H., and Davies, A. J. M. [Saskatoon, Saskatchewan, Canada] *Ann. Surg.*, **118**:154-157. 1943.

An exceptionally large fibroma of the scalp in a 23 year old male was excised. The surgical procedure is described.—W. J. B.

Personal Experiences in the Management of Cutaneous Cancer. Saunders, T. S. [Portland, Ore.] *Urol. & Cutan. Rev.*, **47**:481-482. 1943.

A brief communication concerning diagnosis and treatment.—V. F. M.

The Role of Surgery in the Treatment of Malignant Skin Tumors. Slaughter, D. P. [Univ. of Illinois, Coll. of Med., Chicago, Ill.] *Surgery*, **14**:732-746. 1943.

A general discussion.—W. A. B.

Nervous System

Metastasizing Intracranial Tumors. Abbott, K. H., and Love, J. G. [Mayo Clinic, Rochester, Minn.] *Ann. Surg.*, **118**:343-352. 1943.

An intracranial hemangioblastoma eroding the frontal bone together with nodules of a similar histological appearance in the lungs at autopsy, is presented as a case of metastasis of an intracranial tumor to the lungs. A critical review of other reports is included.—W. J. B.

Arachnoidal Fibroblastoma (Meningioma) with Metastases to the Liver. Hamblet, J. B. [Boston City Hosp., Boston, Mass.] *Arch. Path.*, **37**:216-218. 1944.

Report of a case with 4 figures. Two other cases of arachnoidal fibroblastomas with distant metastases are cited from the literature.—J. G. K.

The Diagnosis and Prognosis of Brain Tumors. Horrax, G. [The Lahey Clinic, Boston, Mass.] *Bull. New York Acad. Med.*, **19**:125-131. 1943.

Suspicion of the presence of a brain tumor is usually aroused by the triad of headache, vomiting, and choked discs, but brain abscess, arachnoiditis, hypertension, and a chronic hematoma may simulate tumor almost exactly. The presence of a source of infection, blood pressure studies, trephination, and air studies should aid in diagnosis. The patients who do not have these symptoms or signs may present one of many evidences of disease, which are listed. Benign, encapsulated neoplasms, favorable for enucleation, can usually be localized by objective neurologic signs. The infiltrating gliomas often require ventriculography for localization. Total extirpation of benign growths is urged, and the prognosis is considered good. Even patients bearing a glioma may have a long survival period if a radical extirpation is performed. In the series of patients operated upon by the author, of 191 who survived resection of a benign tumor, 77.6% were returned to useful life.—E. E. S.

Glioblastoma Multiforme of Brain and Spinal Leptomeninges. Report of a Case. Marcuse, P. [Jefferson Davis Hosp., Houston, Tex.] *South. M. J.*, **36**:823-827. 1943.

Case report.—W. A. B.

Meningioma. Case Report. Pilcher, C. [Vanderbilt Univ. Sch. of Med., Nashville, Tenn.] *Ann. Surg.*, **118**:909-912. 1943.

The successful removal of a meningioma weighing 374 gm. is reported.—W. J. B.

Urinary System—Male and Female

Further Report on Proliferative Lesions of the Urinary Tract. Stirling, W. C., and Ash, J. E. [Washington, D. C.] *Urol. & Cutan. Rev.*, **47**:466-468. 1943.

Proliferative lesions of the urinary tract are initiated by chronic infection. Metaplasia may result in cystic or glandular changes, and in some instances at least, these may be traced into a fully malignant lesion.—V. F. M.

Adrenal Heterotopia, Rests and the So-Called Grawitz Tumor. O'Crowley, C. R., and Martland, H. S. [Newark City Hosp. and Off. of Chief Medical Examiner of Essex Co., Newark, N. J.] *J. Urol.*, **50**:756-768. 1943.

Eight instances of adrenal-renal heterotopia with part or all of the adrenal tissue beneath the renal capsule were found in 5,000 consecutive autopsies. Adrenals were absent from their normal positions, and in all cases the anomaly was bilateral. There was no evidence of endocrine disturbances in the group. The authors think it reasonable to assume that some renal hypernephromas may arise from this misplaced tissue.—V. F. M.

The Occurrence of Endometrial Tissue in the Kidney. Case Report and Discussion. Marshall, V. F. [New York Hosp., and Cornell Univ. Med. Coll., New York, N. Y.] *J. Urol.*, **50**:652-656. 1943.

A renal tumor proved to be composed of normal appearing endometrial tissue with a small amount of smooth muscle. Several possible theories attempting to explain the occurrence of this type of tissue within the kidney are discussed, a theory based on embryology being favored as the most likely. The condition is very rare.—V. F. M.

Endometriosis of the Uretero-Vesical Orifice. Williams, G. H. [Emory Univ. Sch. of Med., Atlanta, Ga.] *Urol. & Cutan. Rev.*, **47**:554-556. 1943.

A case report, with a brief review of the literature.—V. F. M.

Primary Carcinoma of the Ureter. Jaffe, S. A., and Mendillo, A. J. [Grace Hosp., New Haven, Conn.] *Am. J. Surg.*, **62**:126-133. 1943.

A review of the literature and report of 2 cases.—W. A. B.

Primary Sarcoma of the Ureter. Case Report and Review of the Literature. Rademaker, L. [Peninsula General Hosp., Salisbury, Md.] *Am. J. Surg.*, **62**:402-406. 1943.

A case report and review of the literature.—W. A. B.

Primary Osteogenic Sarcoma of the Bladder. Complete Review of Sarcomata of the Bladder. Crane, A. R., and Tremblay, R. G. [St. John's Hosp., Brooklyn, N. Y.] *Ann. Surg.*, **118**:887-908. 1943.

The literature is reviewed, and 151 cases of primary sarcoma of the bladder are summarized. Included is the report of a case of osteogenic sarcoma of the bladder in which there was phosphatase activity in the alkaline range. The most likely origin of such tumors is from mesodermal remnants of the wolffian body in the region of the trigone. Bladder sarcomas in this series were approximately twice as frequent in males as in females and were most frequent in the first and fifth decades of life. Leiomyosarcomas and fibrosarcomas occurred most often, and the area of the trigone was most frequently involved. Because of the high incidence of local infiltration without distant spread, complete cystectomy is the treatment of choice.—W. J. B.

Extramural Rhabdomyosarcoma of the Neck of the Urinary Bladder. Hirsch, E. F. [Chicago, Ill.] *Proc. Inst. Med. Chicago,* **15**:47. 1944.

Brief case abstract. The question is raised whether these tumors are primary in the prostate or whether they develop along the course of the vas deferens.—M. E. H.

Cancerous Mixed Tumor of the Urinary Bladder. Hirsch, E. F., and Gasser, G. W. [Chicago, Ill.] *Proc. Inst. Med. Chicago,* **15**:46. 1944.

Brief case abstract. Only a few reports of cancerous mixed tumors of the urinary bladder have been published.—M. E. H.

Incarcerated Inguinal Hernia Containing a Cancer of the Bladder. Oppenheimer, G. D. [Mt. Sinai Hosp., New York, N. Y.] *J. Urol.,* **50**:784-785. 1943.

A primary carcinoma of the bladder, found in an inguinal hernia, was resected during hernioplasty.—V. F. M.

Gastrointestinal Tract

A Rational Approach to Resection of Carcinoma of the Upper Two-Thirds of the Thoracic Esophagus. Adams, H. D. [Boston, Mass.] *Lahey Clin. Bull.,* **3**:121-123. 1943.

The author concludes that all preliminary procedures in these cases should be reduced to the simplest and the shortest, until it is well established that the lesion is favorable for resection.—M. E. H.

The Re-Establishment of Esophagogastric Continuity Following Resection of Esophagus for Carcinoma of Middle Third. Garlock, J. H. [Mt. Sinai Hosp., New York, N. Y.] *Surg. Gynec. & Obst.,* **78**:23-28. 1944.

Clinical discussion, with description and diagrams of technic, and report of an illustrative case.—J. G. K.

Carcinoma of the Esophagus. Woodward, F. D. [Univ. of Virginia Med. Sch., Charlottesville, Va.] *South, M. J.,* **36**:590-592. 1943.

A general discussion.—W. A. B.

Transthoracic Resection of Esophagus and Stomach for Carcinoma: Report of Two Cases. Clagett, O. T., and Wiig, L. M. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.,* **18**:337-344. 1943.

In presenting their experience with this type of operation, the authors report the second and third cases of successful transthoracic resection of the stomach and esophagus with esophagogastrostomy performed at the Mayo Clinic.—J. L. M.

Transthoracic Subtotal Gastrectomy and Esophagectomy for Cancer. Report of a case. Pack, G. T., and Watson, W. L. [Memorial Hosp., New York, N. Y.] *Arch. Surg.,* **46**:930-938. 1943.

A case report with a description of a prethoracic dermatoesophagoplasty procedure.—W. A. B.

Cancer of the Stomach Arising in Gastritis. Alvarez, W. C. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.,* **18**:225-226. 1943.

The case is reported of a man who had mild abdominal discomforts with low gastric acidity and much gastric mucus at intervals for 15 years. He then became worse and was found to have ulcerative gastritis involving the whole stomach. Nineteen months later he died of carcinoma of the stomach.—J. L. M.

Problems in Gastric Diagnosis. The Gastroscope as a Supplementary Aid to X-Ray Examination. Cohn, A. L., and Levitin, J. [Mt. Zion Hosp., and Univ. of California Med. Sch.] *Gastroenterology,* **1**:841-854. 1943.

Five per cent of early carcinomas of the stomach are not demonstrable roentgenologically. Other lesions of the gastric mucosa, among them gastritis, granulomas, superficial erosions, and polyps are difficult or impossible to detect by x-rays. Direct examination of the gastric lesions by means of the Schindler flexible gastroscope may provide the information necessary for a proper diagnosis in those cases in which the x-ray method is deficient. Cases in which gastroscopy is especially useful are discussed in the paper under the following headings: differentiation between malignant and benign ulcers, between malignant and benign tumors, polyposis, unexplained gastric hemorrhage, antral spasm, hypertrophic gastritis, and "postoperative stomach."

The use of the gastroscope is contraindicated when there is an obstructive lesion of the esophagus, esophageal diverticula, varices, mediastinal tumors, or aneurysm. Three blind areas that can not come under inspection with the gastroscope are the lesser curvature of the antrum, the posterior wall near the cardia, and a small area of the mid-portion of the greater curvature.—A. C.

Aseptic Gastric Resection for Ulcer and Carcinoma. Culligan, L. C. [Minneapolis, Minn.] *Minnesota Med.,* **26**:833-834. 1943.

Peritonitis is the leading cause of death following resection for ulcer and carcinoma. A review of the literature for resection of the stomach for ulcer showed that among 576 cases operated upon there were 33 deaths. Thirteen of these, or 39% were due to peritonitis. In the collected series of 3603 resections for carcinoma of the stomach there were 522 deaths: Of these, 236, or 45%, were due to peritonitis.

Contrasted with this is a series of approximately 410 resections for both ulcer and carcinoma done by the aseptic closed method. In this group there were 2 deaths attributable to peritonitis. One of these was due to subdiaphragmatic abscess following a difficult resection in which it was necessary to open the duodenum. A method of aseptic resection of the stomach using the Furniss clamp is described.—J. L. M.

Technic of Gastric Resection for Carcinoma. Fallis, L. S. [Henry Ford Hosp., Detroit, Mich.] *Surg. Clin. North Am.,* **23**:1259-1268. 1943.

A step by step description of the operation for gastric carcinoma as practiced at the Henry Ford Hospital is outlined. The essential features of a radical operation for gastric carcinoma are believed to be (a) removal of the entire great omentum and superior leaf of the mesocolon, and (b) ligation of the right gastro-epiploic and left gastric arteries at the point of origin. The necessity for a more radical approach in gastric ulcer is pointed out.—J. L. M.

Total Gastrectomy for Carcinoma of the Stomach. Graham, R. R. [Toronto, Canada] *Arch. Surg.,* **46**:907-914. 1943.

An operative technic is described. Of 21 patients subjected to total gastrectomy 7 had no metastases in the regional lymph nodes.—W. A. B.

Palliative Operations for Carcinoma of the Stomach. Gray, H. K., and Shepard, V. D. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **18**:113-118. 1943.

The survival rates in all cases of carcinoma of the stomach in which exploratory operation, palliative gastroenterostomy, or palliative gastric resection was performed at the Clinic from 1907 through 1938 were reviewed, and the results tabulated.

Of the 801 patients who left the hospital after palliative gastroenterostomy 23% were alive at the end of 1 year, and of the 150 patients who left the hospital after palliative partial gastric resection 45% were alive at the end of 1 year.

The authors point out that local extension alone or extension by metastasis to neighboring organs or to lymph nodes draining the stomach is not a contraindication to palliative gastric resection whenever possible or to palliative gastroenterostomy when palliative resection is not feasible.—J. L. M.

Chronic Atrophic Gastritis and Cancer of the Stomach. Guiss, L. W., and Stewart, F. W. [Memorial Hosp., New York, N. Y.] *Arch. Surg.*, **46**:823-843. 1943.

A careful study was made of approximately 300 fixed stomachs removed at operation or within 2 to 3 hours after death. Group A consisted of 35 stomachs from stillborn infants, and infants who died soon after birth. In group B were 73 "normal" stomachs from persons with no evidence of gastric disease; to this group were added 22 specimens from young subjects who died of electric shock. Group C included 77 "normal" stomachs from patients who died of nongastric cancers. Group D was composed of 73 gastric carcinomas. Group E was a miscellaneous group of unselected stomach specimens resected for gastric lesions other than carcinoma. Fourteen specific features were studied including mucosal thickness, rugae and mammillation, type of gland and constituent cells, leukocytic infiltration, intestinal metaplasia, etc.

A normal stomach was described as one with a mucosal thickness of about 1 mm. It may or may not present mammillation and rugae are usually present. It may contain a few lymphoid collections and lymph follicles along the muscularis mucosae. Leukocytic infiltrate may vary from slight to moderate without regard to type of cells present as long as the covering mucosa shows no erosion. Intestinal metaplasia, pyloric gland heterotopia, mucosal cysts, and interglandular fibrosis are absent. The factors included in the concept of chronic atrophic gastritis are mucosal atrophy, increased amounts of leukocytic infiltrate and lymphoid aggregates, intestinal metaplasia, and pyloric gland heterotopia. Variation in one factor tends to be associated with proportionate changes in the others.

Microscopic evidence of chronic atrophic gastritis was present in 82% of stomachs from apparently normal persons over 40 years of age, in 66% of stomachs from persons over 40 who died of extragastric cancer, and in 97% of stomachs with gastric carcinoma. The study does not support the view that chronic atrophic gastritis is a precancerous lesion.—W. A. B.

Total Gastrectomy for Malignancy. Marshall, S. F., and Zintl, W. [Lahey Clinic, Boston, Mass.] *Surg. Clin. North Am.*, **23**:902-914. 1943.

Experience and surgical judgment are necessary in the selection of patients with advanced carcinoma of the stomach who would be benefited by total gastrectomy. Removal of the omentum is suggested, along with splenectomy as indicated in selected cases. Total gastrectomy is consistent with life. Digestion and nutrition can be maintained, and reasonable health may be expected.

The operative mortality in 55 cases was 32.7% (18 patients). A few patients are reported to be well 2, 3, 4, and 5 years following total gastrectomy.—J. L. M.

Curability of Gastric Carcinoma. Methany, D. [Seattle, Wash.] *Northwest Med.*, **42**:17-18. 1943.

The high incidence of gastric carcinoma is remarked. Exploration is urged even when the examiner feels that there is little hope of cure.—E. E. S.

The Duration of Gastric Cancer. Palmer, W. L. [Univ. of Chicago, Chicago, Ill.] *Gastroenterology*, **1**:723-736. 1943.

As a rule, the degree of malignancy of a gastric carcinoma is inversely proportional to the degree of cellular differentiation. Histologically and clinically, cancer of the stomach seems to fall into 2 extreme types. There is an "acute" form, histologically totally undifferentiated, characterized by rapid growth, and a tendency to infiltrate and metastasize. With this type, the prognosis is hopeless regardless of how early the diagnosis is made. The "chronic" form of gastric carcinoma includes circumscribed, polypoid tumors, histologically highly differentiated, and characterized by very slow growth. Here the prognosis is good, even though the diagnosis may be late.

This analysis of gastric carcinoma is supported by the presentation of 5 cases, one of them being reported in great detail. It is concluded that the degree of cellular differentiation appears to be the most important single factor in the prognosis of a case.—A. C.

Transthoracic Resection for Cancer of the Cardiac End of the Stomach. Phemister, D. B. [Univ. of Chicago, Chicago, Ill.] *Arch. Surg.*, **46**:915-929. 1943.

Technic is described, and 10 cases are reported.—W. A. B.

Surgical Care of Patients with Gastric Cancer Before and After Operation. Ravdin, I. S., Royster, H. P., Riegel, C., and Rhoads, J. E. [Hosp. of Univ. of Pennsylvania, and Sch. of Med., Univ. of Pennsylvania, Philadelphia, Pa.] *Arch. Surg.*, **46**:871-878. 1943.

A general discussion.—W. A. B.

Gastroscopic Diagnosis of Gastric Cancer. Schiff, L. [Univ. of Cincinnati Med. Sch. and Cincinnati General Hosp., Cincinnati, Ohio] *Arch. Surg.*, **46**:865-870. 1943.

Among 78 proved cases of carcinoma of the stomach, the tumor was correctly diagnosed in 53 (subsequently 55). The tumor was entirely overlooked in 6 cases and mistaken for another lesion in 9 (subsequently 7). In 10 cases examination was unsatisfactory. In a miscellaneous group, 13 lesions later found to be nonmalignant were mistaken for cancer.—W. A. B.

Sarcoma of the Stomach. A Clinical and Pathologic Study. SCHROEDER, G. F., and SCHATTENBERG, H. J. [Tulane Univ. and Charity Hosp. of Louisiana, New Orleans, La.] *Arch. Surg.*, **47**:8-19. 1943.

A review of the literature and report of 10 cases.—W. A. B.

Pathology of Carcinoma of the Stomach. STOUT, A. P. [Coll. of Physicians and Surgeons, Columbia Univ.; and Presbyterian Hosp., New York, N. Y.] *Arch. Surg.*, **46**:807-822. 1943.

This article is based on the study of 225 resected gastric carcinomas and 185 autopsies of which 42 had been made on patients whose stomachs had previously been resected. Most carcinomas of the stomach arise from the mucus-secreting cells, and the pyloric end of the stomach is most frequently affected. Little emphasis is placed by the author on the microscopic description of types of carcinoma. Grossly, carcinoma of the stomach is described as fungating, ulcerated, spreading, or of no special type. The fungating type, which constitutes only about 10% of all gastric carcinomas, is associated with 50% survival 5 years after resection. Among 15 patients with ulcerated cancers (this type comprised 35.2% of cancers resected from 1936 to 1941) 10 are free from evidences of disease from 2 to 5 years after resection. No case of linitis plastica was encountered in this series, but another form of "spreading carcinoma" was seen 18 times after 1937 and in 15 cases was associated with ulceration. Of the 18 patients, 13 are living and well at unstated periods following resection. Approximately half of the gastric carcinomas removed in the past 5 years could not be assigned to any of the above groups; they were usually late cancers. Lesions of the stomach simulating carcinoma are also discussed.—W. A. B.

Prognosis and End Results in the Treatment of Cancer of the Stomach. WALTERS, W., GRAY, H. K., and PRIESTLEY, J. T. [Mayo Clinic, Rochester, Minn.] *Arch. Surg.*, **46**:939-943. 1943.

Among 10,890 cases of carcinoma of the stomach, seen from 1908 to 1938, 57.3% were clinically considered operable. This percentage increased to 66% in 1942. In the large series, 25.5% of patients had resectable lesions at the time of operation. In 1942 the comparable figure was 36.6%.

The hospital mortality was 16.2% among the 10,890 cases; for the years 1940 to 1941 it was 10.9%. Of patients who survived operation 28.9% were alive after 5 years, and 6.3% lived 25 years or longer. The 5 year survival rate was 43.1% when the regional lymph nodes were not involved, but only 16.5% when they were.—W. A. B.

The Surgical Problem of Gastric Cancer. With Special Reference to: (1) The Closed Method of Gastric Resection, (2) Coincidental Hepatic Resection and (3) Preoperative and Postoperative Management. WANGENSTEEN, O. H. [Univ. of Minnesota Med. Sch., Minneapolis, Minn.] *Arch. Surg.*, **46**:879-906. 1943.

Discussion as indicated in the title.—W. A. B.

Simultaneous Carcinoma and Tuberculosis of the Stomach in a Case of Pernicious Anemia. WHITE, R. R. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **18**:165-172. 1943.

This study is based on a case of pernicious anemia of long standing, in which both carcinoma and tuberculosis of the stomach were found at operation. This is the tenth verified case of gastric tuberculosis encountered at the Mayo Clinic and the second verified case of carcinoma and tuberculosis in the same stomach.—J. L. M.

Lymphosarcoma of the Stomach. YARNIS, H., and COLP, R. [Mt. Sinai Hosp., New York, N. Y.] *Gastroenterology*, **1**:1022-1039. 1943.

Seven cases of small round cell lymphosarcoma and 1 case of reticulum cell sarcoma of the stomach are presented, with special emphasis on the pathologic findings.—A. C.

Lymphosarcoma of the Intestines. USHER, F. C., and DIXON, C. F. [Mayo Clinic, Rochester, Minn.] *Gastroenterology*, **1**:160-178. 1943.

Ewing, writing in 1913, divided lymphosarcoma into 2 types, on a histological basis: (1) malignant lymphosarcoma (small round cell sarcoma) presumably originating from lymphocytes, and (2) reticulum cell sarcoma (large round cell sarcoma) assumed to derive from the reticulum cell of the germ centers of lymphoid tissues. The purpose of the present paper is to evaluate such a classification from a clinical standpoint, especially in relation to prognosis and treatment.

The material for the investigation consisted in all tumors of the large and small intestines, available for study in the records of the Mayo Clinic, that had been unequivocally diagnosed as reticulum cell sarcoma or malignant lymphosarcoma. In each of the 50 cases selected, multiple blocs were recut from the specimen. Diagnosis based on microscopic features was readily made, and the tumors studied were found to fall in equal number into Ewing's 2 histological groups. Distribution of the tumors according to site was as follows: jejunum, 38%; cecum, 36%; rectum, 20%; and colon, 6%. The incidence was greater in males than females, the ratio being about 2:1. Grossly the lesion was either a polypoid growth protruding into the lumen of the intestine, most often in the cecum, or an annular, diffuse cuff-like infiltration of the wall of the bowel, the latter form being prevalent in the small intestine.

Certain symptoms were fairly characteristic. Colicky pain was rather common, with loss of weight, secondary anemia, and a palpable abdominal tumor.

As regards prognosis and response to treatment, either by surgery, irradiation, or a combination of the two methods, no difference was found between reticulum cell sarcoma and small round cell sarcoma. The site of occurrence of the tumor seems to have a greater significance, the average survival time after treatment being 8 years when the tumor was located in the cecum, 2 years in the rectum, and 9 months in the small intestine.—A. C.

Lymphosarcoma of the Intestines. 15 Cases; Characteristic Sigmoidoscopic Picture. WINKELSTEIN, A., and LEVY, M. H. [Mt. Sinai Hosp., New York, N. Y.] *Gastroenterology*, **1**:1093-1099. 1943.

A general study of the disease, based on the study of 15 cases observed at the Mount Sinai Hospital between 1932 and 1942.—A. C.

Multiple Carcinoid Tumors of the Small Intestine: Report of Case. PENNINGTON, R. E., and PRIESTLEY, J. T. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **18**:49-51. 1943.

This case is reported because of the large number of

tumors that were present and because of the prolonged palliation that has already been obtained for the patient. This serves to emphasize the slow growing nature of the tumors and the fact that they should be removed surgically when the opportunity presents itself even though irremovable metastatic lesions are present.—J. L. M.

Leiomyosarcoma of the Small Intestine. RANKINE, J. A. [Cleveland, Ohio] *Canad. M. A. J.*, **48**:415-419. 1943.

A report of 2 cases. Surgical intervention was followed by peritonitis and death, 8 and 11 days later. A general discussion of the disease is included.—A. C.

Carcinoma of Duodenum. One-Stage Radical Pancreaticoduodenectomy, Preserving the External Pancreatic Secretion. Case Report. CHILD, C. G., III. [New York Hosp., and Cornell Univ. Med. Coll., New York, N. Y.] *Ann. Surg.*, **118**:838-842. 1943.

Report of a case in which there was relative freedom from symptoms for 14 months after operation, followed by a recurrence of the tumor.—W. J. B.

Carcinoma of Suprapapillary Portion of the Duodenum. LAIPPLY, T. C. [Western Reserve Univ., and University Hosps., Columbus, Ohio] *Ohio State M. J.*, **39**:50-51. 1943.

A summary of the clinical and pathologic features of this uncommon tumor in a woman of 73 who had had cholecystectomy and choledocholithectomy 10 years previously.—E. E. S.

Surgical Treatment of Carcinoma of the Papilla of Vater. GRAY, H. K., and SHARPE, W. S. [Mayo Clinic, Rochester, Minn.] *Surgery*, **14**:831-846. 1943.

A review of surgical methods is given. At the Mayo Clinic from 1908 to 1941 transduodenal excision or resection of the neoplasm was done in 8 cases with a mortality of 37.5%. One patient subjected to a modified Whipple two-stage operation died. Palliative procedures in which the origin of the tumor was proved by microscopic examination resulted in 9 deaths among 23 cases (39.1%) but in only 1 death among 20 cases (5%) in which the origin of the tumor was not proved by biopsy. The average length of life following palliative operations in the group of 23 cases was 12½ months.—W. A. B.

Carcinoma of the Papilla of Vater. STERNFELD, E., and MEFFLEY, W. H. [Toledo, Ohio] *Ohio State M. J.*, **39**: 436-438. 1943.

The authors present a very precise clinical pattern of this condition indicating that they believe differentiation from tumors arising in the head of the pancreas, contiguous portion of the duodenum, or terminal part of the common duct can be established by this means. A patient thought to have such a tumor is described. It is stated that the clinical diagnosis was confirmed by biopsy, but the histologic distinction between carcinoma of the papilla of Vater and carcinoma arising from nearby ducts is not presented. A partial resection of the duodenum and head of the pancreas was performed. There is no description of the location, appearance, or extent of tumor growth as disclosed by the operation, nor is the surgical specimen described. A biliary fistula developed, and the patient died at home following disruption of his wound. There is no mention of performance of an autopsy.—E. E. S.

Primary Carcinoma of the Infra-Ampullary Portion of the Duodenum. With Example of Probable Origin from Aberrant Pancreatic Tissue. DUFF, G. L., FOSTER, H. L., and BRYAN, W. W. *Arch Surg.*, **46**:494-503. 1943.

A review of the literature and presentation of a case.—W. A. B.

Primary Adenocarcinoma of the Jejunum with Intussusception. Case Report. O'DONOGHUE, J. B., LICHTENSTEIN, M. E., and JACOBS, M. B. [Cook County Hosp., Chicago, Ill.] *Am. J. Surg.*, **63**:382-387. 1944.

The carcinoma occurred in a 24 year old male. Resection with end to end anastomosis was done, and the patient survived.—W. A. B.

Angiofibroma of the Ileum. Clinical Picture in Tumors of the Small Intestine. LICHTENSTEIN, M. E., and DUTRA, F. R. [Northwestern Univ. Med. Sch., and Norwegian-American Hosp., Chicago, Ill.] *Arch. Surg.*, **47**:69-75. 1943.

The paper gives a brief review of the literature on benign tumors of the small intestine, and the first description of an intestinal angiofibroma.—W. A. B.

Carcinoid Tumors (So-Called) of the Ileum. Report of Thirteen Cases in Which There was Metastasis. DOCKERTY, M. B., and ASHBURN, F. S. [Mayo Clinic, Rochester, Minn.] *Arch. Surg.*, **47**:221-246. 1943.

Of 130 carcinomas of the small intestine, there were 30 so-called carcinoid tumors of which 13 had metastasized. The chief symptoms were those of chronic intestinal obstruction. In 2 patients the lesions were found at autopsy. In 3, exploration only was done; in 5, primary resection and in 2 ileocolostomy and secondary resection was performed; and in 1 ileocolostomy alone was done. In 5 of the 10 cases in which accurate information was available the tumors were multicentric. There were metastases to regional lymph nodes in 11 cases and to the liver in 5.

Among the 11 cases in which operation was performed, 1 patient died several days after biopsy of an inoperable tumor, 2 died 2 and 5 years after operation, apparently of recurrence, and the remaining 8 were alive and well for from 10 months to 19 years even though several had hepatic metastases.—W. A. B.

Carcinoid Tumor of the Cecum with Metastasis. POTTER, E. B., and DOCTER, J. M. [King County Hosp., Seattle, Wash.] *Am. J. Path.*, **20**:143-147. 1944.

Case report with 4 figures. The metastases were both local and distant. The authors suggest that the term "carcinoma of the carcinoid type" be substituted for the term "carcinoid" in such instances.—J. G. K.

Pseudomyxoma Peritonei. HINSON, A. [Station Hosp., Will Rogers Field, Okla.] *Am. J. Surg.*, **62**:134-137. 1943.

Most cases of pseudomyxoma peritonei arise as a result of the perforation of pseudomucinous cystadenomas of the ovaries; a few from perforation of mucoceles of the appendix. In the latter case, the most likely theory of formation is that repeated attacks of inflammation eventually cause stenosis of the base of the appendix, and mucus continues to be secreted. Rupture of the mucocele results in dissemination in the peritoneal cavity. In pseudomyxoma peritonei originating from rupture of an

ovarian cystadenoma, the exudate is alkaline, cellularity and papillary formation are conspicuous and the prognosis is poor, while in pseudomyxoma peritonei arising from an appendiceal mucocele the exudate is acid, there are comparatively few cells, and the prognosis is better. Treatment of the latter type should consist of appendectomy with removal of all the gelatinous material possible. The results of irradiation are poor. A case report is presented.—W. A. B.

Cancer of the Bowel. Some Remarks on Diagnosis and Treatment. Dixon, C. F. [Univ. of Minnesota Grad. Sch., Rochester, Minn.] *Wisconsin M. J.*, **43**:618-621: 656. 1944.

The author emphasizes the all important point of early diagnosis by discussing clinical and roentgenologic diagnostic aids. The general discussion of treatment includes preoperative and postoperative care of the patient.—M. E. H.

Diffuse Polyposis of the Large Intestine. McLaughlin, C. W., Jr. [Univ. of Nebraska Coll. of Med., Omaha, Nebr.] *Am. J. Surg.*, **62**:258-266. 1943.

Discussion and report of a case.—W. A. B.

Operative Treatment of Cancer of the Large Bowel Without Colostomy. Babcock, W. W., and Bacon, H. E. [Temple Univ., Philadelphia, Pa.] *Arch. Surg.*, **46**:253-264. 1943.

A description of technic for the restoration of the fecal stream through a functional perineal anus without destroying the radical nature of the operation for cancer.—W. A. B.

Treatment of Large Bowel Obstruction. Transverse Colostomy—Incidence of Incompetency of Ileocecal Valve; Experience at the University of Minnesota Hospitals. Dennis, C. [Univ. of Minnesota Sch. of Med., Minneapolis, Minn.] *Surgery* **15**:713-734. 1944.

A general discussion and operative technic.—W. A. B.

The Diagnosis and Treatment of Carcinoma of the Colon. Wilson, H., [Memphis, Tenn.] *J. Tennessee M. A.*, **36**:47-49. 1943.

A brief summary of some of the well recognized symptoms and signs of carcinoma arising in the right and left portions of the colon is presented. The author's preference in surgical procedures suitable for each situation is outlined.—E. E. S.

Mikulicz Resection for Carcinoma of the Right Colon. Fallis, L. S. [Henry Ford Hosp., Detroit, Mich.] *Surg. Clin. North Am.*, **23**:1269-1278. 1943.

The right colon is eminently suitable for application of the Mikulicz plan of resection for tumors involving this portion of the intestine because of the constancy of the vascular pattern and the facility with which mobilization of the ileocecal segment can be effected. The Mikulicz principle is indicated when obstruction is present, or when resection has to be performed on an unprepared patient. The only real drawback to the operation, irritation of the skin around the temporary ileostomy, is easily controlled.

The steps of the operation are described and are diagrammatically illustrated.—J. L. M.

Extraperitoneal Resection with Temporary Catheter Colostomy for Cancer of the Colon Below the Splenic Flexure. Mayo, C. W., and Twyman, R. A. [The Mayo Clinic, Rochester, Minn.] *Surg. Clin. North Am.*, **23**:1126-1143. 1943.

This article summarizes the authors' experience during a 10 year period (1933 to 1943 inclusive) in 176 consecutive cases in which extraperitoneal resection was performed at the Mayo Clinic.

With recent refinements in preoperative and postoperative care, the operative mortality (7.4% for the series reported) can be kept at a low level. The risk of this procedure is slightly greater (about 2%) when it is performed only as a palliative procedure.—J. L. M.

The Differentiation of Endometriosis and Carcinoma of the Sigmoid Colon. Jenkinson, E. L., and Brown, W. H. [Med. Sch., Northwestern Univ., Chicago, Ill.] *Minnesota Med.*, **26**:773-779. 1943.

A review of the clinical, laboratory, and roentgen characteristics of most of the constricting lesions of the sigmoid colon.—J. L. M.

Endometrioma of the Sigmoid. Smith, R. S. [Brigham City, Utah] *Northwest Med.*, **42**:192-195. 1943.

Symptoms, methods of diagnosis, and operative treatment are reviewed. A case is reported illustrating the difficulty of differentiating between endometrioma and scirrhous carcinoma.—E. E. S.

Polyps of the Rectum and Colon. Their Etiology, Clinical Significance, and Treatment. Brust, J. C. M. [Syracuse Univ. Med. Center Hosp, Syracuse, N. Y.] *New York State J. Med.*, **42**:973-977. 1942.

Present-day opinion regarding adenomas of the rectum and colon is summarized. During the period from 1936 to 1941, the author carried out complete sigmoidoscopic examinations on 4,000 patients and found polyps in 212. These figures do not include persons suffering from hereditary multiple polypoid disease, nor those with multiple polyps or pseudopolyps that were clearly on an inflammatory basis. Three cases are reported, and problems posed by the disease are discussed.—J. L. M.

Cancer of the Left Colon and Rectum. Murdoch, R. L. [Oklahoma City, Okla.] *South. M. J.*, **36**:685-691. 1943.

A general discussion, with brief case studies. Nineteen patients with carcinoma of the left colon were subjected to operation, 16 by a two-stage modified Mikulicz exteriorization procedure. There was 1 postoperative death and 6 deaths from recurrence less than 3 years after operation.

Eighty-seven patients with carcinoma of the rectum and rectosigmoid were operated upon, 46 by the Nutes Procedure. There were 8 postoperative deaths and a survival rate of 56.3% for those patients with tumors resected 4 to 2 years previously.—W. A. B.

Late Invasion of Bladder and Prostate in Cancer of the Rectum or Rectosigmoid Following Abdomino-Perineal Resection. Oppenheimer, G. D. [Mt. Sinai Hosp., New York, N. Y.] *Ann. Surg.*, **117**:456-467. 1943.

The author reviewed 50 consecutive autopsy reports on patients with cancer of the rectum and found invasion of the bladder recorded in 21 cases. Since urinary com-

plications are receiving more attention now in the postoperative care of patients with carcinoma of rectum and rectosigmoid, 9 case reports are given in which late invasion of the bladder occurred with or without involvement of prostate and seminal vesicles. Surgical and radiation therapy are described.—W. J. B.

One Stage Combined Abdominoperineal Resection for Carcinoma of the Rectum. Results of Three Year Follow-Up Survey in Ninety Cases. Mayo, C. W., and Twyman, R. A. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin,* **18**:438-443. 1943.

A follow-up study was made in 90 cases in which the patients survived one stage combined abdominoperineal resection. At the end of 3 years, 61 patients were living and 29 had died. Eleven operations were considered palliative in nature; 79 were done with a view to cure. In the latter group, 56 patients (71%) were living 3 years or more after operation. In the palliative group, 5 patients (45%) were alive 3 years after operation.

The presence or absence of metastasis to local lymph nodes has an important bearing on the prognosis. Involvement of nodes was noted in 44 cases (49%). In the 45 cases without nodal involvement in which operation was performed with a view to cure, 39 patients (87%) survived 3 years or more; however, the presence of involved nodes gave the patient only a 50% chance of living at least 3 years. Even though obvious metastasis to the liver or deep aortic nodes existed at the time of exploration, 45% of the patients survived 3 years or more.—J. L. M.

The Spread of Carcinoma of the Rectum: Invasion of Lymphatics, Veins and Nerves. Seefeld, P. H., and Bargen, J. A. [Mayo Clinic, Rochester, Minn.] *Ann. Surg.,* **118**:76-90. 1943.

One hundred specimens of rectal carcinoma removed at operation were studied. Lymphatic involvement occurred in 47 of the cases, perineural invasion in 30, and venous invasion in 20. The percentage of involvement increased with the increase in the degree of malignancy of the carcinoma (Broders' and Dukes' classifications). Pain was a prominent symptom in 89% of cases where nerves were invaded. Local recurrence was more frequent in cases with invasion of both nerves and veins, but there were twice as many local recurrences with neural involvement alone as with invasion of veins alone. Visceral metastatic lesions were most frequent when there was venous invasion. In 7 cases there was recurrence even though extension to nodes, nerves, or veins was not found at operation.—W. J. B.

One-Stage Perineo-Abdominal Operation for Cancer of the Rectum. Singleton, A. O. [Univ. of Texas, Galveston, Tex.] *Surgery,* **14**:691-701. 1943.

A description of technic.—W. A. B.

Epidermoid Carcinoma of the Anus and the Rectum. Cattell, R. B., and Williams, A. C. [Lahey Clinic, Boston, Mass.] *Arch. Surg.,* **46**:336-349. 1943.

Squamous cell carcinoma occurred 10 times among approximately 600 cases of malignant anal or rectal neoplasm (1.7%). In 2 of these 10 cases metastases were demonstrated in the tissue removed at operation. All cases were treated by operation only. Three patients died: 1 postoperatively, 1 of recurrence in the wound, and 1 in whom a colostomy alone had been done. One patient was living with metastases, 4 were well from 6 months to 3 years and 4 months after operation, and 2 were well 6 and 10 years after treatment. Abdominoperineal resection with radical dissection of the inguinal lymph nodes is advocated for every operable growth. Irradiation is indicated for inoperable lesions and for recurrences.—W. A. B.

Liver

Primary Carcinoma of the Liver. A Clinical-Pathologic Report of Fourteen Cases at the University Hospital from 1927 to 1943. Cunningham, R. M. [Sch. of Med., Univ. of Maryland, Baltimore, Md.] *Bull. School Med., Univ. Maryland,* **28**:61-79. 1943.

Primary carcinoma of the liver is discussed, and the literature is reviewed. Fourteen cases with autopsy reports, from the records of the University Hospital are presented. In 8 cases the clinical course was marked by coma. This did not include coma associated with shock or infection. The nonprotein nitrogen level in 4 cases was abnormally high. The relationship between liver disease, kidney damage, and the hepatorenal syndrome is mentioned briefly.—J. L. M.

Hepatoma in Infancy and Childhood. Discussion Report of Patient Treated by Operation. Packard, G. B., and Stevenson, A. W. [Denver Children's Hosp. and Univ. of Colorado Med. Sch., Denver, Colo.] *Surgery,* **15**:292-306. 1944.

General discussion and report of the successful resection of a hepatoma in a 13 month old child. There was no evidence of recurrence after 15 months.—W. A. B.

Primary Carcinoma of the Liver. Wilbur, D. L., Wood, D. A., and Willett, F. M. [Stanford Univ. Sch. of Med., San Fancisco, Calif.] *Ann. Int. Med.,* **20**:453-485. 1944.

A clinical discussion based on a study of 49 cases.—J. G. K.

Polyposis of the Gall Bladder. Report of a Case Diagnosed Preoperatively by Roentgenologic Examination. Grego, J. G., and Harkins, H. N. [Henry Ford Hosp., Detroit, Mich.] *Am. J. Surg.,* **63**:398-401. 1944.

Case report.—W. A. B.

Bone and Bone Marrow

Hemangioma of Vertebra with Compression of Cord. Report of a Case Cured with Radiation Fourteen Years Ago. Blackford, M. L. [Emory Univ. Sch. of Med., and Piedmont Hosp., Atlanta, Ga.] *J. A. M. A.,* **123**:144-146. 1943.

Sixty-five cases of hemangioma of the vertebra resulting in compression of the cord have been assembled from the literature. In 12 of these, cure was reported from the use of roentgenotherapy alone. The subject of this report, 18 years of age, who received roentgenotherapy 3 months after the onset of symptoms, has subsequently enjoyed 14 years of good health.—M. E. H.

Osteogenic Sarcoma of Vertebrae Secondary to Paget's Disease. Report of Three Cases with Compression of Spinal Cord and Cauda Equina. CAMPBELL, E., and WHITFIELD, R. D. [Albany Hosp., and Albany Med. Coll., Albany, N. Y.] *New York State J. Med.*, **43**:931-938. 1943.

Although the vertebrae are among the more frequent sites of osteitis deformans, malignant neoplastic change therein has seldom been recorded. The authors report 3 cases, one unconfirmed, one of chondrosarcoma, and one of osteogenic sarcoma.—J. L. M.

Generalized Ossifying Chondromata. FRASER, L. W. [Royal Society of Medicine, London, England] *Proc. Roy. Soc. Med.*, **37**:87. 1944.

Description of a case.—E. L. K.

Sacrococcygeal Chordoma with Metastases. GRAF, L. [Coll. of Physicians and Surgeons, Columbia Univ., New York, N. Y.] *Arch. Path.*, **37**:136-139. 1944.

Report of a case in which the very large sacrococcygeal tumor metastasized to the regional lymph nodes, liver, lungs, pleura, and the skin of the right leg and thigh. Four figures illustrate the growth, and 10 similar cases are cited in the literature.—J. G. K.

Osteochondroma of the Base of the Skull. KING, L. S., and BUTCHER, J. [William Beaumont General Hosp., El Paso, Tex.] *Arch. Path.*, **37**:282-285. 1944.

Case report.—J. G. K.

Giant Cell Tumor of the Patella. Case Report. LEVINE, M. A. [Coll. of Med. Evangelists and Cedars of Lebanon Hosp., Los Angeles, Calif.] *Am. J. Surg.*, **62**:286-289. 1943.

—W. A. B.

Ossifying Chondroma Replacing the Infrapatellar Pad of Fat. ROTH, P. B. [London, England] *Proc. Roy. Soc. Med.*, **37**:279-280. 1944.

Description of a case.—E. L. K.

Role of the Chemical Laboratory in Diagnosis of Neoplastic Diseases of Bone. WOODWARD, H. Q. [Memorial Hosp., New York, N. Y.] *Arch. Surg.*, **47**:368-383. 1943.

Metabolism of bone is briefly reviewed, and laboratory methods for the determination of elements in serum and urine, useful in establishing diagnosis of bone disease, are presented.

Among the bone diseases occurring in childhood and youth—the benign cartilage and bone tumors, solitary bone cysts, benign giant cell tumors, endothelioma of bone and inflammatory disease of bone—there is little or no change in blood and urine findings save for an increase in the serum alkaline phosphatase that usually occurs with osteogenic sarcoma and with rickets.

More conspicuous changes occur in the blood and urine constituents of adults with bone disease. With osteolytic metastatic disease the serum alkaline phosphatase, serum inorganic phosphorus, and total serum calcium are normal or high, and there is a high excretion of calcium in the urine, while in osteoplastic disease (including prostatic) the alkaline phosphatase is high, but phosphorus and calcium are normal, and there is no excess excretion of calcium in the urine.

In carcinoma of the prostate with metastases to bone, the serum acid phosphatase is conspicuously elevated in 70% of cases. Plasma cell myeloma is associated with normal or increased serum alkaline phosphatase, serum proteins, phosphorous, and calcium, and the appearance in the urine in 60% of cases of the characteristic Bence-Jones protein. In osteomalacia, though the serum alkaline phosphatase is increased, the phosphorus, calcium, and serum proteins are usually decreased. Hyperparathyroidism is identified by the pronounced elevation of serum alkaline phosphatase and serum and urinary calcium, and diminished level of phosphorus. In osteitis deformans an elevated alkaline phosphatase alone is found, while in senile osteoporosis there are no changes of significance.—W. A. B.

PANCREAS

Resection of the Pancreas: Discussion of Special Problems. CATTELL, R. B. [Lahey Clinic, Boston, Mass.] *Surg. Clin. North Am.*, **23**:753-766. 1943.

Special problems concerned with the diagnosis and surgical removal of the pancreas and duodenum for carcinoma are discussed. It is re-emphasized that at times pancreaticoduodenal resection must be carried out without a confirmed diagnosis of malignancy because of the inadequacy of biopsy and frozen section. Technical steps in both the one- and two-stage operations are presented. Attention is directed to the importance of avoiding a pancreatic fistula, either internal or external, and methods of prevention are shown.—J. L. M.

Dermoid Cyst of Pancreas. Case Report. DECOURCY, J. L. [DeCourcy Clinic, and Good Samaritan Hosp., Cincinnati, Ohio] *Ann. Surg.*, **118**:394-395. 1943.

A case of pancreatic dermoid cyst is added to the 2 cases previously reported by others. The defect, after removal of the cyst, was covered by a strip of omentum.—W. J. B.

Islet Cell Carcinoma of Pancreas, with Metastasis. HANNO, H. A., and BANKS, R. W. [Univ. of Pennsylvania, Philadelphia, Pa.] *Ann. Surg.*, **117**:437-449. 1943.

The literature on islet cell tumors of the pancreas is reviewed, and 21 cases with involvement of other organs are analyzed in greater detail. A case report with autopsy findings is added to the list of cases of islet cell carcinoma with metastases. The primary site of the neoplasms is not confined to any one portion of the pancreas. The microscopic picture in primary and metastatic lesions is similar to that of the islands of Langerhans. Of 11 patients, 2 had a history of diabetes previous to the progressive hypoglycemia present in every case. Survival periods ranged from 3½ weeks to 4½ years.—W. J. B.

Unusual Cases of Hyperinsulinism and Hypoglycemia. HOLMAN, E., WOOD, D. A., and STOCKTON, A. B. [Stanford Univ. Sch. of Med., San Francisco, Calif.] *Arch. Surg.*, **47**:165-177. 1943.

Four cases are presented. (1) In the first case, an extrapancreatic islet adenoma was responsible for the symptoms; an adenoma of the tail of the pancreas was removed, but the patient's symptoms of hypoglycemia (varying from tingling in the mouth to complete unconsciousness) returned. Reoperation was done and a second islet tumor was removed from the region between the pancreas and the spleen. An uneventful recovery followed. (2) In a second patient at autopsy an islet adenoma was found in the wall of the duodenum, which

had apparently been associated with no functional disturbance. (3) Carcinoma presumably may develop on the basis of an old calcified adenoma; at autopsy a third patient was found to have widespread carcinoma of the islets of Langerhans with a tumor 12 cm. in diameter containing a centrally calcified area 3.5 cm. in diameter in the tail of the pancreas. Prodromal symptoms were present for 14 years before the occurrence of symptoms unmistakably due to hyperinsulinism, which then progressed rapidly during 2 years before death. It is believed that the calcified portion represented a long-standing adenoma that produced but small amounts of insulin, and that concomitantly with "carcinomatous change" the output of insulin increased. (4) The fourth, rather bizarre case, was that of a woman of 40 years who had typical signs and symptoms of hypoglycemia with blood sugar values as low as 33 mgm. per 100 cc. A laparotomy was done and the pancreas, separated from all surrounding structures except the blood vessels, was thoroughly explored, but no adenoma was found. The patient made an uneventful recovery and had no further symptoms of hypoglycemia. No explanation for this unexpected result can be offered.—W. A. B.

The Diagnosis of Carcinoma of the Pancreas. Kiefer, E. D., and Moravec, M. [Lahey Clinic, Boston, Mass.] *Surg. Clin. North Am.*, **23**:738-746. 1943.

This is a review based on a study of 74 cases of pancreatic carcinoma, in all of which the diagnosis was confirmed by laparotomy. Diagnostic criteria for patients with and without jaundice are considered.—J. L. M.

Total Pancreatectomy for Carcinoma. Case Report. Rockey, E. W. [Portland, Oregon] *Ann. Surg.*, **118**: 603-611. 1943.

In a case of pancreatic adenocarcinoma, the pancreas was removed together with the duodenum and lower stomach. A cholecystojejunal and a gastrojejunal anastomosis were made. Death occurred on the 15th postoperative day, and leakage of the stump of the common bile duct was found at autopsy. Implantation of the common duct into the jejenum is suggested as a better operative procedure since a secondary blood supply would thus be provided.—W. J. B.

Leukemia, Lymphosarcoma, Hodgkin's Disease

Acute Lymphatic Leukemia in Childhood. Falkenstein, D., and Fowler, W. M. [State Univ. of Iowa, Coll. of Med., Iowa City, Iowa] *Am. J. Dis. Child.*, **65**:445-454. 1943.

A review of 61 consecutive cases of acute lymphatic leukemia.—C. J. M.

Oral Lesions in the Leukemias. FitzGerald, L. M. [Dubuque, Iowa] *J. Iowa State Med. Soc.*, **33**:424-426. 1943.

A report of 9 cases of leukemia. Lesions of the buccal cavity, varying from pyorrhea alveolaris or hemorrhages of the tonsils to frank gangrenous gingivitis were encountered in all but one of these cases. The exception was a subleukemic lymphatic leukemia.—A. C.

The Varying Clinical Picture of Leukemia. Third Edwin R. Kretschmer Memorial Lecture. Haden, R. L. [Cleveland, Ohio] *Proc. Inst. Med. Chicago*, **15**:98-104. 1944.

The author has analyzed the histories, physical examinations and blood studies of 250 patients suffering from leukemia. The greatest variety of clinical pictures was encountered; correlation of the laboratory findings with the clinical aspects of the disease is most important.—M. E. H.

Monocytic Leukemia Associated with Bone Changes. Kositchek, R. J. [Los Angeles, Calif.] *Ann. Int. Med.*, **19**:1008-1013. 1943.

Case report. The osteolytic changes were similar to those seen in other types of leukemia.—J. G. K.

Morphologic Obliteration of Chronic Myeloid Leukemia by Active Tuberculosis. Report of a Case. Heinle, R. W., and Weir, D. R. [Western Reserve Univ. Med. Sch., and Lakeside Hosp., Cleveland, Ohio] *Am. J. M. Sc.*, **207**:450-453. 1944.

The case is reported as presenting further evidence that tuberculosis may have a profound influence on the clinical and pathologic features of chronic myeloid leukemia.—J. G. K.

Leucemia and Pregnancy. A Case Report and Review of the Literature. McGoldrick, J. L., and Lapp, W. A. [Kings County Hosp., Brooklyn, N. Y.] *Am. J. Obst. & Gynec.*, **46**:711-718. 1943.

The case is reported of a woman with chronic myelogenous leukemia, who was delivered of a still-born infant. The literature is reviewed. Congenital leukemia has been observed, but in no instance has the child of a leukemic mother shown evidence of the disease at birth. A bibliography of 94 references is appended.—A. K.

Infiltration of Bone with Spontaneous Fracture in a Case of Chronic Myelogenous Leukemia. Meyer, L. M., Friedman, A. B., and Ginsberg, V. [Kings County Hosp., Brooklyn, N. Y.] *Arch. Surg.*, **46**:514-517. 1943.

Case report.—W. A. B.

Primary Intracranial Lymphosarcoma. A Report of Two Cases and Review of the Literature. Abbott, K. H., and Adson, A. W. [Mayo Clinic, Rochester, Minn.] *Arch. Surg.*, **47**:147-159. 1943.

—W. A. B.

Lymphosarcoma: A Statistical Study and Evaluation of Treatment. Howes, W. E., and Levin, B. [Brooklyn Cancer Inst., Brooklyn, N. Y.] *Radiology*, **40**:565-580. 1943.

A study of lymphosarcoma at the Brooklyn Cancer Institute included 47 patients, of whom 13 are living from 2 to 6 years. Nine have no evidence of disease after treatment by surgery, irradiation, or both. Four patients with disseminated disease have had palliation for from 2 to 6 years. When the disease is localized, treatment is restricted, but when the disease is generalized not only obvious areas but mediastinal and retroperitoneal areas should be treated. The authors believe 3,000 r to the tumor within 3 weeks is necessary to sterilize.—R. E. S.

Generalized Lymphosarcomatosis with Marked Involvement of the Brain. Radzinski, J. M., and Uznanski, M. E. [Chicago, Ill.] *Illinois M. J.*, **85**:87-89. 1944

Case reported because of the unusual cerebral and meningeal involvement and the fulminating clinical course of the disease.—M. E. H.

The Surgical Treatment of Malignant Lymphoma. Gall, E. A. [Massachusetts General Hosp., Boston, Mass.] *Ann. Surg.*, **118**:1064-1070. 1943.

Forty-eight cases of malignant lymphoma, in which

radical excision of the lesion was performed, were analyzed. There was agreement with the age and sex distribution of the disease found in a larger series previously reported by the authors. Five patients died soon after operation. Eighteen of 19 patients have been without signs and symptoms for 3 or more years. There was recurrence in 23 cases, with death in 13. Postoperative prophylactic irradiation was carried out in 21 cases, with recurrence in 8, no recurrence in 10, and result unknown in 3. In this group the average duration of life from the onset of the disease was 6.9 years, and the average postoperative survival period was 5.2 years. Both figures are significantly greater than corresponding values for the group with other treatment. This is of particular interest since there was complete localization of the lymphomatous lesion in 10% of 135 autopsies, although many lesions were not amenable to surgery or recognized clinically.—W. J. B.

Hodgkin's Disease Complicated by Amyloidosis and a Nephrotic Syndrome: Case Report. LEHMAN, R. G. [San Diego, Calif.] *Ohio State M. J.*, **39**:232-233. 1943.

Report of a case.—E. E. S.

Hodgkin's Disease. The Incidence, Distribution, Nature and Possible Significance of the Lymphogranulomatous Lesions in the Bone Marrow. A Review with Original Data. STEINER, P. E. [Univ. of Chicago, Chicago, Ill.] *Arch. Path.*, **36**:627-637. 1943.

Lymphogranulomatous foci in the bone marrow were found in one or more sections of various bones selected at random in 11 of 14 consecutive cases of Hodgkin's disease. The author suggests that these obscure lesions may be responsible for pain, but it seems doubtful to him that they cause severe anemia by replacing the marrow. The distribution of the lesions in Hodgkin's disease resembles more closely the distribution of the reticulo-endothelial than that of the lymphatic system—an observation that suggests that the disease should be regarded as a disorder of the reticulo-endothelium.—J. G. K.

THYMUS

Transitional Cell Carcinoma of the Thymus in a Child. Follow-Up Report. AUFSES, A. H. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **10**:423-425. 1943.

In 1934, when this case was originally reported, the patient had been given a course of x-ray therapy and had shown noticeable improvement. Subsequently, there was a recurrence of symptoms, followed by a partial operative removal of the tumor and later, a fatal termination.—A. Cnl.

Thymic Tumors in Myasthenia Gravis. CLAGETT, O. T., and EATON, L. McK. [Mayo Clinic, Rochester, Minn.] *Surg. Clin. North Am.*, **23**:1076-1082. 1943.

Eight cases are reported in the literature in which thymic tumors (not to be confused with persistent or hyperplastic thymic tissue) have been removed surgically in the treatment of myasthenia gravis. In these 8 cases, 3 patients died too soon after operation for the effect on the myasthenic symptoms to be observed, leaving only 5 cases for evaluation from this point of view. Two patients were apparently improved, 2 experienced complete remissions, and 1 was not benefited. Since December 1941, 5 thymic tumors have been removed in cases of myasthenia gravis at the Mayo Clinic. Two patients, who had thymic tumors, were operated on during remissions apparently induced by roentgen irradiation, and they have remained well. In 2 other cases the course of the myasthenia gravis apparently was not influenced. The fifth patient has been operated on too recently for the results to be evaluated. There have been no deaths, and the 2 patients failing to respond satisfactorily have not been affected deleteriously by the procedure.—J. L. M.

THYROID

Carcinoma of the Thyroid Gland with a Solitary Metastasis to the Skull. Report of a Case. ALBRIGHT, H. L. [Boston Univ. Sch. of Med., Boston, Mass.] *New England J. Med.*, **230**:573-576. 1944.

A case report of a patient with carcinoma of the thyroid gland and a single skull metastasis, who showed no evidence of recurrence 2½ years after surgical removal of both lesions. Pertinent references are given.—C. W.

So-Called "Benign Metastasizing Goiter." Report of Two Cases with Intracranial Metastasis. FRIEDMAN, H. H. [Jewish Hosp., Brooklyn, N. Y.] *Arch. Surg.*, **46**:377-385. 1943.

A brief review of the literature.—W. A. B.

A New Concept Regarding the Origin of So-Called Primary Carcinoma of the Hyperplastic Thyroid. GOETSCH, E. [Long Island Hosp., and Long Island Coll. of Med., Brooklyn, N. Y.] *Ann. Surg.*, **118**:843-858. 1943.

Carcinoma of the thyroid rarely appears in diffuse toxic goiter. Nine of these rare cases were studied; in 3 the neoplasms were found to occur in very small fetal adenomas hidden in the hyperplastic gland. It is probable that carcinoma in exophthalmic goiter occurs even less frequently than is reported in the literature.—W. J. B.

Three Cases of Longevity with Carcinoma of the Thyroid. HIRSCH, E. F., and MILLER, J. L. [St. Luke's Hosp., Chicago, Ill.] *Illinois M. J.*, **85**:92-94. 1944.

Three cases presented at Clinical Pathological Conference.—M. E. H.

Pulsating Tumors of the Sternum and Occiput Due to Metastatic Carcinoma of the Thyroid Gland. MOLLE, W. E. [Cincinnati, Ohio] *Ohio State M. J.*, **39**:346-347. 1943.

The paper gives a brief review of the literature and reports a case considered the sixth of its kind to be described. The patient lived 8 years after metastases had been demonstrated in the lungs. After death the carcinoma was found also in skull, kidneys, and mesentery. The only other tumor likely to give rise to pulsating sternal masses is said to be the hypernephroma.—E. E. S.

Hyperparathyroid Disease Due to Tumor of the Parathyroid. RICE, C. O. [Minneapolis, Minn.] *Minnesota Med.*, **26**:1092-1093. 1943.

Case report.—J. L. M.

Congenital Teratoma of the Thyroid. Sutton, P. W., and Gibbs, E. W. [Coll. of Med. of Univ. of Cincinnati, and the Children's Hosp., Cincinnati, Ohio] *Am. J. Surg.*, **63**:405-407. 1944.

A case report concerning a congenital teratoma of the thyroid successfully removed from a 3 months old infant. This is the thirty-first authentic case reported.—W. A. B.

Multiple Tumors

Multiple Carcinomas of the Stomach. Report of a Case. Brindley, G. V., Dockerty, M. B., and Gray, H. K. [Mayo Clinic, Rochester, Minn.] *Proc. Staff Meet., Mayo Clin.*, **18**:193-199. 1943.

A review of the literature and the authors' series of cases indicate that multiple simultaneous gastric carcinomas are rare. Among 1,184 cases of carcinoma of the stomach, operated upon at the Mayo Clinic between January 1, 1932, and December 31, 1941, 23, or 1.94%, were multiple gastric carcinomas. There was no case similar to the one reported here, in which resection of about three-fourths of the stomach was performed, thus removing 4 adenocarcinomas. The lesions were of grades 4, 3, 2, and both 1 and 2 respectively (Broders' classification). Diffuse chronic gastritis may have been a precursor of these multiple carcinomatous lesions. Here multicentric tumors are accepted as an example of multiple primary tumors.—J. L. M.

Multiple Primary Malignant Tumors. McNamara, F. P., Dubuque, Iowa] *J. Iowa State Med. Soc.*, **33**:264-266. 1943.

A report of 7 cases of multiple primary malignant tumors found in a series of 909 necropsies in which the incidence of malignant neoplastic disease was 24%. In each of these 7 cases different groups of organs were affected.—A. C.

Carcinoma and Leukemia: Report of Two Cases with Combined Lesions: Review of Literature. Morrison, M., Feldman, F., and Samwick, A. A. [Jewish Hosp., Brooklyn, N. Y.] *Ann. Int. Med.*, **20**:75-84. 1944.

Adenocarcinoma of the rectum and myeloblastic leukemia were present in one of the two cases; carcinoma of the head of the pancreas and chronic lymphatic leukemia were present in the other.—J. G. K.

Multiple Primary Carcinomata. Whigham, J. R. M. [London, England] *Proc. Roy. Soc. Med.*, **37**:233-234. 1944.

An account of 4 cases, with a discussion.—E. L. K.

Cancer Control and Public Health

The Role of the Cancer Clinic in Cancer Control. Crowell, B. C. [Chicago, Ill.] *Radiology*, **40**:539-542. 1943.

More than 380 cancer clinics meeting the minimum standards of the American College of Surgeons are now established in the United States. The minimum standards for cancer clinics are tabulated.—R. E. S.

Organizational Structure and Activities of State Cancer Programs. Hawkins, J. W. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:347-350. 1944.

In 38 states cancer control programs are conducted by official agencies of the state government. Educational activities predominate. In the last 2 years, the budget for cancer has doubled; the budget for the fiscal year 1942-43 totaled $2,066,900.33, of which 97% was in the 14 states having cancer legislation. The development of leadership for cancer programs and the promotion of appropriate control legislation appear to be the most important steps in the establishment of adequate state cancer control programs.—Author's summary.

A Tumor Clinic for Patients of Moderate Means. Holmes, G. W. [Massachusetts General Hosp., Boston, Mass.] *Radiology*, **40**:554-556. 1943.

At the Massachusetts General Hospital a medical staff conducts a free tumor clinic in the morning and a pay clinic for patients of moderate means in the afternoon, the same space and facilities being utilized. When surgery is advised the patient is referred to the surgical department. Fees are moderate and thus the patient of limited income has an opportunity for receiving medical service not available heretofore. The earnings, after deduction of expenses, are divided among the staff members.—R. E. S.

Experiences and Results in Tumor Clinic Organization in New York State. Kress, L. C., and Levin, M. L. [New York State Dept. of Health, Albany, N. Y.] *Radiology*, **40**:543-548. 1943.

There are now 37 tumor clinics in upstate New York, organized to bring cancer facilities within reach of the entire population of the state. Postgraduate courses in cancer education are sponsored, and most of the clinics are approved by the American College of Surgeons.—R. E. S.

Practical Aspects of Tumor Clinic Management. Uhlman, E. [Michael Reese Hosp., Chicago, Ill.] *Radiology*, **40**:557-560. 1943.

At the Michael Reese Hospital the tumor clinic has separate departments for each specialty. Meetings and consultations are held regularly. The author feels that the chairman of such a group should be the radiotherapist. When there is controversy over the type of treatment to be given, the final decision is made by the representative of the department concerned, who is serving on the tumor clinic staff.—R. E. S.

The Role of the Surgeon in the Tumor Clinic. Wolfer, J. A. [Northwestern Univ., Chicago, Ill.] *Radiology*, **40**:549-553. 1943.

A well organized tumor clinic should have a competent staff including a radiologist, pathologist, internist, dermatologist, and well trained surgical group. The role of the surgeon in cases of early cancer is particularly important.—R. E. S.